Université de Montréal

Substrats neuronaux de la mémoire épisodique et de la mémoire de travail dans le vieillissement normal et pathologique

par

Francis Clément

Département de psychologie
Faculté des Arts et Sciences
Option Neuropsychologie Recherche/Intervention

Thèse présentée à la Faculté des études supérieures
en vue de l'obtention du grade de
Philosophiæ doctor (Ph. D.) en psychologie

Mai 2011

Université de Montréal

Faculté des études supérieures

Cette thèse intitulée :

Substrats neuronaux de la mémoire épisodique et de la mémoire de travail dans le vieillissement normal et pathologique

présentée par :

Francis Clément

A été évaluée par un jury composé des personnes suivantes :

Président rapporteur : Franco Lepore

Directrice de recherche : Sylvie Belleville

Examinateur interne : Maryse Lassonde

Examinateur externe : David A. Bennett

Représentant du doyen de la FAS : Annie Angers

SOMMAIRE

La maladie d'Alzheimer (MA) est de loin le type de démence le plus répandu chez les personnes âgées. Il est maintenant possible de proposer un certain nombre d'interventions ou de stratégies préventives aux personnes portant un diagnostic de MA ou à risque de développer la maladie. Il est donc important de diagnostiquer cette maladie le plus tôt possible. Les personnes avec un trouble cognitif léger (TCL) représentent une population d'intérêt puisqu'elles sont à haut risque d'évoluer vers une démence et plusieurs d'entres elles seraient ainsi dans une phase prodromale de la MA.

Les travaux de cette thèse visent à explorer les activations fonctionnelles associées à la mémoire épisodique et à la mémoire de travail dans le TCL ainsi qu'aux effets de la sévérité de la maladie et des caractéristiques de la tâche sur ces activations. Dans un premier temps, nous exposerons les connaissances relatives au niveau des atteintes cognitives, du patron d'activation fonctionnelle et des plus récents modèles élaborés pour expliquer les changements d'activation dans le vieillissement normal et pathologique (Chapitre 1). Par la suite, les études réalisées dans le cadre de cette thèse seront présentées. Nous avons d'abord étudié la fiabilité du signal d'activation chez les TCL et chez les personnes âgées saines (PA) à l'aide de tâches d'encodage et de récupération de mots (Chapitre 2). Nous avons ensuite comparé le patron d'activation cérébral des PA et des personnes TCL alors qu'elles réalisaient une tâche d'encodage et de récupération de mots. L'effet de la sévérité a été évalué en corrélant les activations des personnes TCL à leurs scores obtenu à une échelle évaluant leur cognition globale (Chapitre 3). L'effet de sévérité a ensuite été étudié de manière plus approfondie chez un plus grand nombre de TCL en utilisant la médiane du groupe à cette même échelle

pour déterminer un groupe de TCL plus atteints et un groupe de TCL moins atteints. Ces deux groupes ont ensuite été comparés à un groupe de PA lors d'une tâche d'encodage de paires de mots reliés sémantiquement ou non-reliés (Chapitre 4), une tâche de reconnaissance de paires de mots mesurant principalement la familiarité ou principalement la recollection (Chapitre 5), ainsi que deux tâches impliquant des composantes différentes de la mémoire de travail et des fonctions exécutives, soit la manipulation de l'information et l'attention divisée (Chapitre 6).

Les résultats présentés dans cette thèse ont mis en évidence une distinction entre le patron d'activation des TCL et des PA qui semble caractérisée par une interaction entre le niveau de sévérité de la maladie et les processus cognitifs impliqués dans la tâche. L'effet de sévérité a été observé lors de plusieurs tâches impliquant des processus cognitifs différents où les MCI moins atteints ont montré principalement des hyperactivations sous-tendant des mécanismes compensatoires et les MCI plus atteints ont montré principalement des hypoactivations soulignant la dégradation de ces mécanismes. Par ailleurs, les résultats de nos études ont aussi montré que cet effet de sévérité est modulé par le moment d'altération du processus cognitif impliqué dans la tâche: les processus altérés précocément dans le TCL sont caractériséees par des hyperactivations chez les TCL moins atteints tandis que les processus altérés plus tardivement ont plutôt élicité des hyperactivations chez les TCL plus atteints. Les implications de ces résultats, ainsi que les limites des études, sont discutés (Chapitre 7).

Mots clés : trouble cognitif léger, maladie d'Alzheimer, compensation, neuroimagerie, mémoire épisodique, fonctions exécutives, cognition.

ABSTRACT

Alzheimer's disease (AD) is by far the type most common dementia in the elderly. It is now possible to propose a number of interventions or preventive strategies to individuals with a diagnosis of AD or at risk of developing the disease. It is therefore important to diagnose this disease as soon as possible. Individuals with mild cognitive impairment (MCI) represent a population of interest as they are at high risk of developing dementia and many of these persons might thus be in a prodromal phase of AD.

The work of this thesis aims to explore the functional activations associated with episodic memory and working memory in MCI as well as studying the effects of disease severity and of task characteristics on these brain activations. Initially, we will review the current knowledge about the level of cognitive impairment, functional activation pattern and the more recent models developed to explain changes of functional activation in normal aging and disease (Chapter 1). Subsequently, the studies of this thesis will be presented. First, we studied the reliability of activation signal in people with MCI and healthy elderly individuals (HE) using tasks of encoding and retrieval of words (Chapter 2). We then compared the pattern of brain activation between HE and MCI persons while they were administered tasks of encoding and retrieval of words and pseudo-words. The effect of severity was assessed by correlating activations of MCI persons with their scores on a scale assessing their overall cognition (Chapter 3). The effect of severity was then examined in more details in a larger number of people using the median score of the MCI group on the scale of global cognitive assessment to determine a group of less impaired MCIs and a group of more

impaired MCIs. These two groups were compared to a group of HE while conducting a task of encoding semantically related or unrelated pairs of words (Chapter 4), a recognition task of word pairs measuring either mainly familiarity processes or recollection processes (Chapter 5) and two tasks involving different components of working memory or executive functioning, the manipulation of information and division of attention (Chapter 6).

The results presented in this thesis have highlighted a distinction between the functional activation pattern of MCI persons and HE which seems to be characterized by an interaction between level of disease severity and the cognitive processes involved in the task. The effect of severity was observed in several tasks involving different cognitive processes during which less impaired MCIs showed primarily hyperactivations underlying compensatory mechanisms and more impaired MCIs showed mainly hypoactivations suggesting a degradation of these mechanisms. Moreover, the results of our studies have also shown that the effect of severity is modulated by the time of alteration of the cognitive processes involved in the task: the process altered early in MCI are caracterized by hyperactivations in less impaired MCIs while processes that are altered later on elicited hyperactivations in more impaired MCIs. The implications of these findings and the limitations of the studies are discussed (Chapter 7).

Keywords : mild cognitive impairment, Alzheimer's disease, compensation, brain imaging, episodic memory, executive functions, cognition.

TABLE DES MATIÈRES

Liste des tableaux

CHAPITRE 2

CHAPITRE 3

CHAPITRE 4

CHAPITRE 5

CHAPITRE 6

Liste des figures

CHAPITRE 2

CHAPITRE 3

CHAPITRE 4

ANNEXE I

Liste des abréviations

AD: Alzheimer's disease

ANCOVA: analysis of covariance

ANOVA: analysis of variance

BA: Brodmann's area

BEM: Batterie d'Efficience Mnésique

BOLD: blood oxygen level-dependent

CDR: Clinical Dementia Rating scale

CÉS-RNQ: Comité conjoint d'Évaluation Scientifique du Regroupement de Neuroimagerie du Québec

CIHR: Canadian Institute of Health Research

DTA: démence de type Alzheimer

EPI: Eysenck Personality Inventory

fMRI: Functional Magnetic Resonance Imaging

FQRNT: Fond Québécois de la Recherche sur la Nature et les Technologies

FRSQ: Fonds de Recherche en Santé du Québec

GDS: Geriatric Depression Scale

GE-EPI: Gradient-Echo Echo-Planar imaging sequences

GSES: Generalized self-efficacy scale

HAROLD: Hemispheric asymmetry reduction in older adults

HERA: Hemispheric encoding/retrieval asymmetry

ICC: Intraclass correlation

IUGM: Institut Universitaire de Gériatrie de Montréal

MA: maladie d'Alzheimer

MANCOVA: multiple analysis of covariance

MANOVA: multiple analysis of variance

MAP: Mesure d'Actualisation du Potentiel

MCI: mild cognitive impairment

MDRS: Mattis Dementia Rating Scale

MMSE: Mini-Mental State Examination

MNI: Montreal Neurological Institute

MOCA: Montreal Cognitive Assesment Scale

MRI: Magnetic Resonance Image

N.S.: non significant

OARS: Older Americans Resources and Services

PA: personnes âgées saines

PD: Parkinson's disease

PGC-MS: Philadelphia Geriatric Center Morale Scale

PIB: Pittsburgh Compound B

PSI: Psychiatric Symptom Index

QAM: Questionnaire d'Auto-évaluation de la mémoire

RFX: random effects analysis

RL/RI-16: Rappel Libre/Rappel Indicé à 16 Items

ROI: region of interest

SD: standard deviation

SMAF: Functional Autonomy Measurement System

SPM: Statistical Parametric Mapping

TCL: trouble cognitif léger

TEP: Tomographie par Émission de Potisons

UNF: Unité de Neuroimagerie Fonctionnelle

WAIS: Weschler Adult Intelligence Scale

À ma famille,

qui m'a appris la richesse et la grandeur de l'être humain

REMERCIEMENTS

Avant toute chose, je tiens à remercier sincèrement ma brillante directrice de recherche, Sylvie Belleville. Notre relation étudiant-superviseure a été d'une telle richesse et a tellement évolué au cours des années, que la décrire prendrait autant de pages que cette thèse. En effet, celle-ci est tellement intense, que l'on peut aisément la comparer à notre propre période de développement. Initialement, j'ai été un enfant qui a admiré son mentor et qui a bu chacune de ses paroles; puis un adolescent qui l'a contestée et qui a essayé de lui prouver qu'il pouvait être son égal; enfin, un jeune adulte qui a redécouvert la valeur de son mentor et qui l'a suppliée de reprendre ses enseignements. J'espère maintenant devenir un collègue et un ami qui pourra redonner à son tour. Merci Sylvie de m'avoir transmis ta passion pour la recherche, la clinique et le travail d'équipe.

J'adresse un merci spécial à Samira et Émilie pour leur soutien tant professionnel que personnel. Je n'aurais jamais pu accomplir tout ce travail sans leur aide essentielle tant au niveau du testing que des analyses. Je les remercie aussi de m'avoir soutenu et encouragé dans les moments difficiles et d'avoir célébré avec moi les moments heureux. Merci aussi à Marcelo, Johanne et Marc du service informatique, sans qui cette thèse serait probablement écrite à la main sur du papyrus! Merci pour votre patience lors de mes nombreux combats contre Endnote, Office et Matlab.

Un gros merci aux membres de mon laboratoire qui sont maintenant devenus des amis très précieux avec qui, je l'espère, je partagerai des liens pendant encore de

nombreuses années. Sara, Véronique, Marie-Claude, Sylvia, Lyssa, Stéphanie, Chloé, Frédéric, Simona, Anne-Sophie et Bianca, vous avez été les meilleurs collègues qu'une personne puisse espérer et le seul fait de vous avoir rencontré confirme le choix judicieux d'avoir fait ce Ph.D. À ceux et celles qui n'ont pas encore terminé, j'espère pouvoir vous aider à mon tour.

Je tiens aussi à remercier très chaleureusement mes superviseurs d'internats et de stages, Paule, Élaine, Danny, Chantal et Stéphanie qui m'ont enseigné leur amour pour le travail clinique et leur volonté de venir en aide aux gens souffrants. Mon contact avec vous aura changé ma vie d'une manière que je commence à peine à réaliser.

Je ne pourrai jamais remercier suffisamment ma famille et mes amis pour leur soutien durant cette étape importante de ma vie. Vous êtes ce que j'ai de plus précieux et je me considère extrêmement chanceux d'avoir un réseau social aussi riche, tant en nombre qu'en qualité. Un merci particulier à ma sœur qui se trouve dans les deux catégories et qui me donne ainsi une double dose d'amour et d'encouragement.

Enfin, un énorme merci aux participants qui sont les vrais auteurs de cette thèse et qui nous font don de leur temps et de leur patience. Votre générosité ne sera jamais suffisamment louangée.

CHAPITRE 1

Introduction générale

1.1 La maladie d'Alzheimer et le trouble cognitif léger

1.1.1 La maladie d'Alzheimer

La démence est une réduction acquise des capacités cognitives qui entraîne une baisse du fonctionnement et une perte d'autonomie. La démence peut avoir plusieurs étiologies. Parmi celles-ci, la démence de type d'Alzheimer (DTA) est de loin celle la plus répandue chez les personnes âgées, affectant environ un Canadien sur vingt âgé de plus de 65 ans (McDowell et al., 1994), et représente la cinquième cause de décès de cette population. Selon le rythme actuel de progression, on estime qu'en 2050 de 11 à 16 millions d'américains souffriront de cette maladie neurodégénérative si aucun traitement curatif n'est découvert (Mebane-Sims, 2009). L'impact de cette maladie sur notre société est majeur, tant au niveau social qu'économique et cet impact continuera d'augmenter avec l'explosion appréhendée du nombre de personnes atteintes.

Selon les critères du DSM (American Psychiatric Association, 2000), le diagnostic de la DTA repose sur la présence d'un déclin significatif et progressif au niveau des fonctions mnésiques et d'au moins un autre domaine cognitif (fonctions exécutives, langage, gnosies ou praxies). Les déficits cognitifs doivent être suffisamment importants pour occasionner une diminution significative du fonctionnement social ou professionnel. Ils ne peuvent s'expliquer par une affection d'une autre nature qu'elle soit organique (neurologique, tumorale, métabolique, infectieuse ou toxique) ou psychique (dépression, confusion mentale, schizophrénie, etc.). Selon les critères de recherche du NINCDS-ADRDA, un patient souffre d'une maladie d'Alzheimer (MA) probable s'il montre une détérioration progressive de la

mémoire et d'une autre fonction cognitive, incluant préférablement une atteinte du fonctionnement, une histoire familiale de la maladie et la présence d'atrophie à la tomodensitométrie cérébrale (McKhann et al., 1984). Selon ces critères, une MA certaine n'est diagnostiquée que lorsqu'il y a confirmation neuropathologique associée à la symptomatologie clinique propre à la MA probable. Les critères diagnostiques actuels de la MA comprennent donc la présence d'une atteinte relativement importante de la cognition et dont l'impact fonctionnel est déjà visible et plusieurs estiment que pour rencontrer ces critères la maladie doit avoir déjà occasionné des dommages cérébraux importants. Or, vu la prévalence et l'impact social de cette maladie, il apparaît nécessaire d'en identifier les signes le plus précocement possible si l'on désire prévenir, ou du moins retarder l'impact de la maladie ainsi que dans l'éventualité d'un traitement curatif. Les patients pourraient ainsi bénéficier d'un éventuel traitement le plus rapidement possible. Pour cela, les récentes études ont permis d'élaborer des critères permettant d'identifier des individus qui apparaissent comme étant particulièrement à risque de développer la maladie et qui pourraient en présenter des signes très précoces. Ces personnes sont désignées comme ayant un trouble cognitif léger.

Le trouble cognitif léger

Il est maintenant connu que la MA s'installe bien avant que les patients ne rencontrent les critères diagnostiques de la maladie. Les individus dans cette période dite « prodromale » de la MA manifestent des atteintes cognitives dont ils peuvent se plaindre. L'identification de cette période prodromale est cruciale, car malgré l'absence

de traitement curatif, il est maintenant possible de proposer un certain nombre d'interventions pharmacologiques (Petersen *et al.*, 2005) ou de stratégies préventives (Belleville, Gilbert et al., 2006) aux personnes portant un diagnostic de MA ou à risque de développer la maladie. De plus, avec les avancées actuelles dans le domaine de la neuropharmacologie, il pourrait éventuellement devenir possible d'arrêter l'avancée des atteintes neuropathologies dès qu'elles seront détectées.

Les chercheurs ont proposé plusieurs types de classification dans le but d'identifier les personnes âgées susceptibles d'être dans ce stade prodromal de la MA (voir Feldman & Jacova, 2005, pour une revue de littérature). Depuis une dizaine d'années, une attention particulière a été dirigée vers la notion de trouble cognitif léger (TCL, ou MCI en anglais). Les critères proposés pour identifier les individus présentant un TCL sont: a) La présence d'une plainte cognitive, corroborée par un proche dans la mesure du possible; b) Une performance sous les valeurs normatives tenant compte de l'âge et de l'éducation dans au moins une tâche mnésique (TCL amnésique domaine simple) ou dans au moins une tâche mnésique et une tâche mesurant un autre domaine cognitif (TCL amnésique domaines multiples); c) L'absence d'altération significative dans le fonctionnement quotidien; d) L'absence de critères d'identification de la démence (Petersen et al., 2001; Petersen et al., 1999; Winblad et al., 2004).

Plusieurs études ont montré que les individus ayant répondu aux critères de TCL ont une plus grande incidence de démence de type Alzheimer. En effet, le taux de progression vers la MA chez les personnes TCL est d'environ 10 à 15% par année, alors qu'il est de 1 à 2% par année chez les personnes âgées saines (Petersen *et al.*,

1999). Ces personnes sont donc à haut risque de développer la maladie et plusieurs d'entre elles pourraient se trouver dans une phase pré-clinique de la MA (Gauthier et al., 2006; Lambon Ralph, Patterson, Graham, Dawson, & Hodges, 2003). Pour ces raisons, l'examen des atteintes cognitives et des fonctions cérébrales chez les personnes avec TCL est susceptible d'apporter un éclairage nouveau et riche en informations sur les phases les plus précoces de la MA. L'examen de la littérature portant sur l'atteinte cognitive dans la MA porte à croire que certains processus de mémoire spécifique tels que la mise en relation des unités d'information, la recollection et certaines sous-composantes de l'administrateur central de la mémoire de travail pourraient être particulièrement atteintes dans les stades les plus précoces de la MA. Pour cette raison, notre travail a porté plus particulièrement sur ces composantes. Dans la prochaine section, les travaux répertoriant les atteintes de la mémoire et des fonctions exécutives dans le TCL seront rapportés et mis en relation avec ceux portant sur la MA (section 1.2). Puis, nous ferons de même pour les travaux ayant fait appel à la neuroimagerie fonctionnelle (section 1.3). Ensuite, nous examinerons si la sévérité de la maladie ou la nature de la tâche pourrait rendre compte des résultats observés au niveau des activations fonctionnelles (section 1.4). Cet examen de la littérature nous amènera vers nos objectifs et hypothèses (section 1.5)

1.2 Atteintes cognitives

1.2.1 Atteintes de la mémoire épisodique dans la MA et le TCL

Les atteintes cognitives dans la MA ont fait l'objet de nombreuses études au cours des deux dernières décennies. La fonction qui a reçu le plus grand intérêt est sans

contredit la mémoire épisodique, la principale fonction cognitive altérée dans la MA. La mémoire épisodique réfère à un système de rétention des évènements et de leur contexte spatio-temporel (Tulving, 2004). On distingue souvent deux étapes en mémoire épisodique: l'encodage et la récupération. Les patients MA semblent présenter de nombreuses difficultés tant pour l'encodage que la récupération de l'information. Ainsi, ils montrent des difficultés à apprendre des listes de mots et, une fois apprises, ils présentent rapidement des difficultés à rappeler les mots ou à les reconnaître parmi des distracteurs (Moulin, James, Freeman, & Jones, 2004; Traykov, Rigaud, Cesaro, & Boller, 2007). De plus et contrairement aux personnes âgées saines, ils bénéficient peu de la présence d'une structure susceptible de supporter l'encodage, par exemple la présence liens sémantiques entre les mots à apprendre (Almkvist 1999). Cette difficulté pourrait s'expliquer par une atteinte sémantique qui les empêcherait d'encoder les indices. Toutefois, elle pourrait aussi provenir du fait que l'encodage de l'item et de son contexte (ici l'indice) nécessite la mise en relation de diverses unités d'informations et que les patients MA auraient de la difficulté à unir ces unités lors de leurs apprentissages. Il s'agirait alors d'une atteinte des processus de mémoire associative. Les études utilisant des tâches de mémoire associative verbale et non-verbale ont d'ailleurs relevé des atteintes particulièrement importantes chez les patients MA autant en mémoire à court terme (Parra et al., 2009) qu'en mémoire à long terme (Sahakian et al., 1988; Swainson et al., 2001). Les études ont aussi démontré que les patients MA sont atteints au niveau de la reconnaissance. Enfin, ils auraient des atteintes importantes au niveau des processus de recollection, c'est-à-dire ceux permettant de récupérer les items ainsi que leur contexte d'encodage, et à un moindre degré, des déficits au niveau des processus de familiarité, ceux reflétant la

reconnaissance qu'un item a été appris sans information sur son contexte d'apprentissage (voir Smith & Knight, 2002, pour une série d'études à ce sujet avec la procédure de dissociation des processus).

Les personnes TCL auraient elles aussi, comme les patients MA, des atteintes touchant les processus d'encodage et de récupération (Perri, Serra, Carlesimo, & Caltagirone, 2007). D'abord, on note la présence de difficultés dans des tâches de rappel libre de listes de mots (Collie & Maruff, 2000; Collie, Maruff, & Currie, 2002; Nordahl et al., 2005; Perri, Carlesimo, Serra, & Caltagirone, 2005; Petersen et al., 1999), dans des tâches de rappel de textes et dans des tâches de rappel de mots pairés (Collie et al., 2002; Dudas, Clague, Thompson, Graham, & Hodges, 2005). Toutes ces tâches font appel autant à l'encodage qu'à la récupération. Notons que, tout comme les patients MA, les TCL bénéficient peu de support à l'encodage, tel que la présence de liens sémantiques entre les mots à apprendre (Perri et al., 2005). Encore une fois, cette difficulté pourrait s'expliquer soit par la présence d'une atteinte sémantique, soit par une atteinte de la mise en relation des unités d'information lors de l'encodage. Étant donné que des atteintes en mémoire associative ont été proposées sur la base d'une difficulté dans le rappel de la localisation spatiale de dessins (Collie et al., 2002) ou de visages (Dudas et al., 2005), il a été suggéré que les difficultés d'encodage des TCL pourraient provenir en grande partie de leur atteinte de la mémoire associative (De Jager, Blackwell, Budge, & Sahakian, 2005; Pereira, Yassuda, Oliveira, & Forlenza, 2008). Dans les tâches de reconnaissance, plusieurs études ont indiqué une altération des processus de recollection chez les personnes TCL, alors que les processus de familiarité semble être encore préservés à ce stade-ci de la maladie (Anderson et al.,

2008; Hudon, Belleville, & Gauthier, 2009; Westerberg et al., 2006) (mais voir Wolk, Signoff, & Dekosky, 2008).

En résumé, les études cognitives de la MA et du TCL exposent un patron d'atteinte en mémoire épisodique qualitativement similaire avec des déficits au niveau de l'encodage et de la récupération; elles montrent aussi des difficultés particulièrement importantes lors des tâches reposant sur l'apprentissage associatif et sur la récupération du contexte (recollection). De plus, la littérature indique que l'utilisation de matériel structuré sémantiquement ne permettrait pas aux patients MA et aux personnes TCL de contrer leurs difficultés. De façon générale, les atteintes sont moins importantes chez les TCL que chez les patients MA indiquant un gradient de sévérité au cours de l'évolution de la maladie.

1.2.2 Mémoire de travail et fonctions exécutives dans la MA et le TCL

La mémoire de travail est un système de rétention qui permet le maintien et la manipulation de l'information à court terme. Certains modèles ont proposé que la mémoire de travail repose sur le fonctionnement d'un ensemble de processus de contrôle attentionnel relativement indépendants tant sur le plan neuroanatomique que cognitif (Belleville, Rouleau, Van der Linden, & Collette, 2003; Miyake et al., 2000). Ainsi, la composante attentionnelle de la mémoire de travail, l'administrateur central (Baddeley, 1996), aurait plusieurs fonctions, telles la capacité à coordonner plusieurs tâches simultanément (attention divisée), à alterner entre plusieurs stratégies cognitives (alternance), à maintenir l'attention sur un stimulus tout en ignorant l'effet distracteur

de d'autres (inhibition), ainsi qu'à maintenir et manipuler de l'information en mémoire (manipulation).

Plusieurs études se sont intéressées aux atteintes exécutives et au dysfonctionnement de l'administrateur central de la mémoire de travail chez les patients MA. Ces études rapportent généralement des atteintes importantes pour la quasi totalité des fonctions de contrôle attentionnel (voir, Bherer, Belleville, & Hudon, 2004, pour une revue de littérature à ce sujet). Concernant la manipulation de l'information, les patients MA ont montré des performances inférieures à celles des personnes âgées saines dans des tâches d'alphaspan (rappel d'une série de mots en ordre alphabétique plutôt que dans l'ordre de présentation (Belleville, Chertkow, & Gauthier, 2007; Belleville et al., 2003), ainsi que dans une tâche d'empan en ordre inversé (Almkvist, Fratiglioni, Aguero-Torres, Viitanen, & Backman, 1999). Les patients MA montrent aussi des atteintes lorsqu'ils doivent diviser leur attention entre deux tâches concurrentes (Belleville et al., 2007; Kalpouzos et al., 2005). De plus, des performances déficitaires ont été relevées dans les épreuves ciblant les fonctions inhibitrices, telles que mesurées par la tâche de Hayling (Belleville, Rouleau, & Van der Linden, 2006) ou avec le test de Stroop (Amieva et al., 2002). En résumé, les patients MA semblent déficitaires dans la grande majorité des tâches exécutives administrées. Leurs atteintes ne semblent donc pas être spécifiques à une composante particulière, mais plutôt généralisées à l'ensemble des fonctions de contrôle attentionnel de la mémoire de travail.

De plus en plus d'études soulignent également la présence d'altérations au niveau de la mémoire de travail dans le TCL. En effet, les personnes TCL montrent des performances déficitaires dans les tâches faisant appel aux fonctions inhibitrices, tel que mesurées par la tâche de Stroop (Belanger, Belleville, & Gauthier, 2010) et par la tâche de Hayling (Belanger & Belleville, 2009; Belleville et al., 2007). Par ailleurs, plusieurs études ont indiqué une atteinte de l'attention divisée (Belleville et al., 2007; Dannhauser et al., 2005; Okonkwo, Wadley, Ball, Vance, & Crowe, 2008) ainsi qu'une altération des processus de manipulation de l'information chez les TCL qui progresseront vers la MA (Belleville et al., 2007). Enfin, une étude a aussi souligné des troubles des processus d'alternance dans le TCL (Belleville, Bherer, Lepage, Chertkow, & Gauthier, 2008). En résumé, les individus TCL montrent des atteintes cognitives dans la plupart des sous-composantes attentionnelles de la mémoire de travail. Ces difficultés pourraient avoir un impact important, car elles peuvent exacerber les problèmes mnésiques (Ranganath, Cohen, & Brozinsky, 2005) et sous-tendre une grande partie des plaintes associées aux tâches quotidiennes complexes (Pereira et al., 2008). De plus, les donnés de plusieurs études suggèrent qu'une détérioration des fonctions de contrôle attentionnel chez les personnes TCL est associée à une progression plus fréquente vers la MA. (Belanger & Belleville, 2009; Belleville et al., 2007; Royall, Palmer, Chiodo, & Polk, 2005).

En résumé, la plupart des sous-composantes de l'administrateur central de la mémoire de travail semblent être déficitaires chez les patients MA et chez les personnes TCL. L'atteinte semble toutefois plus généralisée chez les patients MA, tandis qu'une certaine hétérogénéité des déficits a été observée chez les TCL en

fonction de leur degré de sévérité (Belleville et al., 2007) ou en fonction de leur évolution ultérieure vers la MA.

1.3 Neuroimagerie

L'évaluation neuropsychologique permet d'identifier la spécificité et l'ampleur des atteintes cognitives en examinant les performances des individus sur différentes tâches cognitives. En revanche, la neuroimagerie fonctionnelle examine les patrons d'activités cérébrales associés aux activités cognitives et s'intéressent donc aux réseaux neuronaux utilisés pour accomplir la tâche. La neuroimagerie fonctionnelle apporte des informations intéressantes et complémentaires relatives aux régions cérébrales qui sous-tendent les performances cognitives et sur les processus engagés pour réaliser les tâches cognitives. En comparant le patron d'activation de patients avec des dommages cérébraux à des personnes saines, il devient possible d'obtenir des informations sur la présence et le type de compensation neuronale mis en place par les patients. Dans cette section, nous examinerons les études qui ont porté sur l'encodage de la mémoire épisodique, sur la récupération de la mémoire épisodique et sur la mémoire de travail et les fonctions exécutives. Dans tous les cas, nous rapporterons d 'abord les études portant sur la MA puis celles portant sur le TCL.

1.3.1 Mémoire épisodique - Encodage

Les études en neuroimagerie fonctionnelle qui se sont intéressé à la mémoire ont porté soit sur la phase d'encodage, soit sur la phase de récupération. Parmi les études ayant examiné les activation des patients MA, cinq ont examiné l'encodage

intentionnel ou incident de scènes ou de photos (Golby et al., 2005; Machulda et al., 2003; J. Mandzia, Black, Grady, McAndrews, & Graham, 2002; Rombouts et al., 2000; Small, Perera, DeLaPaz, Mayeux, & Stern, 1999). Ces études ont toutes rapporté des hypoactivations du lobe temporal médian (principalement de l'hippocampe et du gyrus parahippocampique), c'est à dire une activation moins importante chez les MA que chez les contrôles. De plus, certaines ont aussi noté des hypoactivations chez les MA dans la région occipitotemporale (Golby et al., 2005; J. Mandzia et al., 2002), dans le lobe occipital (Golby et al., 2005), dans le lobe frontal (J. Mandzia et al., 2002) et dans le cervelet (Golby et al., 2005). Une seule étude d'encodage rapporte des hyperactivations, c'est à dire une activation plus importante chez les MA que chez les contrôles, dans le lobe pariétal gauche (J. Mandzia et al., 2002). Dans la même veine, Kato et ses collègues ont utilisé un paradigme d'apprentissage de figures géométriques chez 8 PA et 7 MA légers (MMSE > 23) et ont observé que les MA présentaient une hypoactivation du cortex préfrontal ventrolatéral droit (aires de Brodmann 45/46), du gyrus temporal inférieur antérieur gauche (aires de Brodmann 20/21), du gyrus supramarginal droit (aire de Brodmann 40) et du cortex entorhinal droit. Plusieurs études rapportent donc des hypoactivations lors des tâches d'encodage de scènes ou de photos chez les patients avec MA.

Les résultats sont plus divergents lorsqu'une tâche d'association « nom et visage » est utilisée (Dickerson *et al.*, 2005; Pariente *et al.*, 2005; Sperling *et al.*, 2003). Dans les trois études ayant fait appel à ce type de tâche, les auteurs ont noté des hyperactivations du cortex préfrontal chez les patients MA mais des hypoactivations du lobe temporal médian. De plus, deux des études ont observé des hyperactivations au

niveau du lobe pariétal (Pariente et al., 2005; Sperling et al., 2003) et une d'entre elles a noté une hyperactivation du cortex cingulaire postérieur (Sperling et al., 2003).

Puisque les TCL sont à un stade moins sévère de la maladie, leur étude pourrait fournir des informations intéressantes concernant l'évolution des activations dans le décours de la MA. Cependant, les quelques études qui ont étudié l'activation cérébrale associée à l'encodage en mémoire chez des personnes TCL rapportent des résultats contradictoires. Par exemple, certains auteurs rapportent une hypoactivation de l'hippocampe chez les TCL dans une tâche d'apprentissage de dessins d'objets (Johnson et al., 2006) ou de scènes visuelles (Machulda et al., 2003) tandis que d'autres observent une hyperactivation de l'hippocampe (Dickerson et al., 2005; Hamalainen et al., 2007; Kircher et al., 2007). L'équipe de Dickerson rapporte également que l'hippocampe s'active de manière corrélationnelle avec la performance à une tâche d'apprentissage de scènes visuelles (Dickerson et al., 2004). Une meilleure performance était associée à une plus grande activation. Plusieurs études rapportent une hypoactivation du cortex préfrontal chez les TCL (Dannhauser et al., 2008; Elgh, Larsson, Eriksson, & Nyberg, 2003; Johnson et al., 2006; J. Mandzia et al., 2002; J. L. Mandzia, McAndrews, Grady, Graham, & Black, 2007), alors qu'une étude montre une hyperactivation dans ces régions (Kircher et al., 2007).

En résumé, les études de tomographie par émission de positons (TEP) et IRMf qui ont utilisé une tâche d'encodage en mémoire épisodique ont principalement observé une hypoactivation du lobe temporal médian (surtout de l'hippocampe et du gyrus parahippocampique) et du lobe temporal de manière bilatérale ainsi que des

hyperactivations du cortex préfrontal chez les patients MA avec des résultats plus divergents pour les autres régions. Des résultats plus contradictoires ont toutefois été observés chez les TCL puisque certaines études rapportent des hyperactivations alors que d'autres rapportent des hypoactivations et ce, pour les mêmes régions cérébrales (en particulier, l'hippocampe et le cortex préfrontal).

1.3.2 Mémoire épisodique - Récupération

Il existe relativement peu d'études ayant porté sur la phase de récupération en mémoire dans la MA. Une d'entre elles s'est intéressée à la reconnaissance de photographies de divers objets, nombres et mots, ayant été encodées auparavant (Kessler, Herholz, Grond, & Heiss, 1991). Les auteurs ont observé des hypoactivations chez les patients MA dans le gyrus frontal moyen, dans le gyrus temporal supérieur, à la jonction temporo-pariétale, dans V1 et dans le noyau lentiforme. De manière similaire, une étude mesurant la reconnaissance faisant suite à une tâche d'apprentissage répétitive de patrons géométriques abstraits a observé des hypoactivations dans les gyri temporaux moyen et inférieur droit, dans le lobe occipital droit et dans le lobe temporal médian (hippocampe, gyrus parahippocampique, gyri lingual et fusiform) (Gron, Bittner, Schmitz, Wunderlich, & Riepe, 2002). Des hyperactivations ont également été observées dans la MA pour la reconnaissance de photographies d'objets et dessins (J. Mandzia et al., 2002) dans le gyrus frontal inférieur bilatéralement et dans le lobe pariétal. Gron et collaborateurs (2004) ont mesuré les activations associées à la reconnaissance de patrons géométriques abstraits et ont trouvé des hyperactivations dans le cortex préfrontal et dans le lobule pariétal inférieur et des hypoactivations dans le lobe temporal, dans le précuneus, dans le uncus

gauche, dans le noyau caudé antérieur ainsi que dans le lobe temporal médian. Certaines études rapportent à la fois des hyperactivations et des hypoactivations. Une étude TEP en rappel de mots indicé (Backman *et al.*, 1999) et une étude IRMf en reconnaissance d'associations nom-visage (Pariente et al., 2005) rapportent des hypoactivations du lobe temporal médian, des hypoactivations et hyperactivations du lobe temporal et des hyperactivations des lobes pariétaux et frontaux, du noyau cingulaire postérieur et du côté gauche du cerebellum. De manière similaire, l'étude de (Becker *et al.*, 1996), qui porte sur le rappel libre de mots en TEP, rapporte des hypoactivations au niveau du gyrus frontal moyen (aire de Brodmann 10) et des hyperactivations au niveau du cortex préfrontal dorsolatéral (aires de Brodmann 8, 9, 10) et des gyri supramarginaux (aire de Brodmann 40) et angulaires (aire de Brodmann 39).

La littérature actuelle sur les activations cérébrales chez les TCL durant des tâches de récupération épisodique est encore peu développée. Une étude montre une réduction de l'activation dans les régions frontales chez les personnes TCL par rapport aux personnes âgées saines (Elgh et al., 2003). De plus, une étude a démontré que les personnes avec TCL activent moins le cortex cingulaire postérieur que les personnes âgées saines (PA) dans une tâche de reconnaissance de dessins d'objets (Ries et al., 2005). Au contraire, Heun et collaborateurs indiquent une plus grande activation frontale chez les TCL que chez les PA dans une tâche d'apprentissage de noms communs (Heun et al., 2007).

En résumé, les quelques études qui ont utilisé une condition de récupération en mémoire épisodique chez les patients MA convergent vers une hypoactivation du lobe temporal médian (principalement de l'hippocampe et du gyrus parahippocampique) et du lobe temporal (sauf pour deux études) de manière bilatérale dans les deux cas. Les études chez les TCL sont rares et beaucoup plus divergents.

1.3.3 Mémoire de travail et fonctions exécutives

Deux études TEP et trois études IRMf se sont intéressées à la mémoire de travail dans la MA jusqu'à présent. Afin d'évaluer la boucle phonologique, une équipe de chercheurs a demandé à 6 MA de niveau léger ainsi qu'à 6 PA de répéter à voix haute 5 ou 10 mots pendant l'enregistrement TEP et ils ont comparé ces répétitions à une condition contrôle de lecture de mots (Woodard *et al.*, 1998). Au niveau comportemental, les patients et les participants contrôles ont performé aussi bien dans les deux conditions (5 ou 10 mots). Cependant, les MA ont eu besoin d'activer leur cortex préfrontal dorsolatéral (aires de Brodmann 8, 9) bilatéralement tandis que les PA ne l'ont activé que du côté droit. De plus, les MA ont montré des hyperactivations dans les aires médiales droites (aires de Brodmann 6, 32), le gyrus moyen droit (aires de Brodmann 46/9, 6) du cortex préfrontal et le lobule pariétal inférieur gauche (aire de Brodmann 39, gyrus angulaire). Ainsi, pour la même tâche et pour les mêmes performances, les MA ont montré des hyperactivations au niveau de leur cortex préfrontal et de leur gyrus angulaire. Cependant, il est intéressant de noter qu'aucune différence d'activation n'est observée entre les deux groupes lorsque la répétition se limite à trois mots (Becker et al., 1996). Une autre étude a administré une tâche de mémoire à court terme verbale (listes de 4 mots, chacune suivie d'une reconnaissance)

à 16 PA et à 16 patients MA et a observé que les MA avaient des hypoactivations dans le cortex préfrontal, dans le gyrus supramarginal et dans le lobe temporal ainsi que des hyperactivations dans l'hippocampe et dans le gyrus parahippocampique. Les auteurs de cette étude concluent que les patients MA utilisent des mécanismes de reconnaissances alternatifs pour exécuter la tâche.

Des résultats similaires à l'étude de Woodard et collaborateurs (1998) ont été observés dans une tâche de mémoire à court terme avec des chiffres en IRMf: comparativement aux contrôles, les MA ont montré des hyperactivations du gyrus frontal supérieur gauche et de l'uncus gauche (Starr *et al.*, 2005). De plus, de l'hypoactivation a aussi été observée dans leur gyrus parahippocampique. Au niveau de l'administrateur central, une tâche d'attention divisée où les participants devaient porter attention à la fois à un stimulus visuel (un « checkboard » rouge et noir alternant ses couleurs à 7 Hz) et à un stimulus vibrotactile (une stimulation appliquée à la main droite pendant 2 secondes à chaque 4 secondes) a trouvé que les MA hypoactivaient leur cunéus (aire de Brodmann 17) et hyperactivaient et hypoactivaient des structures du tronc cérébral (putamen droit, thalamus gauche et protubérance annulaire droite) (Johannsen, Jakobsen, Bruhn, & Gjedde, 1999). Il faut cependant noter que cette tâche d'attention divisée demandait très peu de ressources cognitives, car aucune diminution de performance n'a été notée chez les PA et les MA lors de la double tâche comparativement aux tâches exécutées individuellement. Finalement, une tâche de 3-Back avec des photos d'objets a été utilisé par Yetkin, Rosenberg, Weiner, Purdy, & Cullum (2005). Encore une fois, les performances des patients MA ne différaient pas de celles des PA. Cependant, de nombreuses différences d'activation ont été notées

chez les MA comparativement aux participants contrôles: hyperactivation du cortex préfrontal, du lobe temporal, du gyrus fusiform droit et du noyau lentiforme droit ainsi qu'une hypoactivation du gyrus précentral gauche, du gyrus frontal supérieur droit et des gyri temporaux inférieurs et fusiforme droit.

Jusqu'à présent, seules deux études ont mesuré les activations fonctionnelles associées à la mémoire de travail chez les personnes avec TCL. Lors d'une tâche de mise-à-jour consistant à détecter si le dernier item présenté est identique à celui présenté trois items auparavant (3-Back de photos d'objets de la vie de tous les jours), Yetkins et son équipe rapportent davantage d'activations frontales et temporales médiales chez les personnes TCL que chez les personnes âgées saines (Yetkin et al., 2005). Le patron inverse a été observé lors d'une étude d'attention divisée dans laquelle les participants devaient à la fois appuyer sur une clé lorsqu'ils voyaient une lettre particulière et appuyer sur une autre clé lorsqu'il entendait un chiffre particulier. Dans cette étude, les TCL ont montré moins d'activité cérébrale dans le cortex préfrontal gauche que les PA (Dannhauser et al., 2005). Ainsi, les deux seules études sur le sujet ont des résultats divergents.

En résumé, les études en mémoire de travail et de fonctions exécutives chez les patients MA sont peu nombreuses et la plupart utilisent des tâches demandant peu de ressources cognitives. Ces études montrent que les patients MA hyperactivent leur cortex préfrontal, et plus particulièrement leur cortex préfrontal dorsolatéral gauche, lors de l'accomplissement de tâche de mémoire de travail et ce, malgré des

performances similaires à celles des sujets sains. Les études chez les personnes TCL sont encore moins nombreuses et montrent des résultats contradictoires.

1.4 Impact de la sévérité sur les résultats en neuroimagerie fonctionelle

Les résultats des études de neuroimagerie fonctionelle (IRMf et TEP) montrent des résultats divergents chez les MA avec toutefois une certaine consistance: plusieurs auteurs rapportent des hyperactivations au niveau du lobe préfrontal et des hypoactivations dans le lobe temporal médian. Il en est tout autre des études chez les TCL, qui rapportent tant des hyperactivations que des hypoactivations et ce, pour les mêmes régions cérébrales. Plusieurs facteurs pourraient expliquer ces divergences. D'une part, le niveau de sévérité de la maladie pourrait être un facteur explicatif. On sait qu'avec l'évolution de la maladie, les lésions se propagent des régions temporales médiales aux régions corticales associatives (pariétales, frontales et temporales) et leur ampleur s'accentue (Braak & Braak, 1991). Il est ainsi possible que ces changements dans l'ampleur et la localisation des dommages puissent mener à l'activation de réseaux neuronaux différents et ainsi à des patrons d'activation différents. Outre le fait que les études divergent considérablement en fonction des caractéristiques des patients recrutés, certaines études apportent un support direct à cette hypothèse. Schröder et ses collègues (2001) ont évalué l'impact du niveau de sévérité de la maladie sur les différences d'activation entre des patients MA et PA à l'aide d'une tâche d'apprentissage verbal sériel. Pour ce faire, ils ont divisé leur groupe de MA en fonction de la sévérité de leur atteinte cognitive telle que mesurée par l'échelle MMSE: ceux dont la sévérité est légère (MMSE > 21) et ceux dont la sévérité est modérée (MMSE < 22). Comparativement aux PA, les deux groupes ont montré une

hypoactivation des gyri inférieurs, moyens et supérieurs du lobe temporal, du gyrus inférieur préfrontal droit et de l'aire 19 du lobe occipital droit. Cependant, les patients dont l'atteinte était modérée montraient des hypoactivations additionnelles au niveau des gyri moyens et supérieurs préfrontaux bilatéralement, du gyrus inférieur préfrontal gauche et des aires 17, 18, 19 et 21 du lobe occipital de manière bilatérale. Ces résultats sont intéressants, car ils soulignent l'évolution du patron d'activation cérébrale en fonction du niveau de sévérité de la maladie et suggèrent que les hypoactivations s'étendent au fur et à mesure du développement de la maladie.

Il est également possible que des mécanismes de plasticité cérébrale agissent en début de maladie quand les lésions sont relativement peu importantes. Ces phénomènes pourraient être particulièrement actifs durant la phase de TCL. Comme cette plasticité ne serait possiblement présente que chez les TCL les moins atteints, la présence ou l'absence de plasticité pourrait expliquer l'hétérogénéité retrouvée dans les travaux portant sur des patients qui sont dans les phases précliniques de la maladie. En effet, dans l'étude de Yetkins et collaborateurs (2005) mentionnée ci-haut, les TCL avaient un score moyen relativement élevé (moyenne de 28) au MMSE et ils ont montré principalement des hyperactivations à une tâche de mise-à-jour tandis que dams l'étude de Dannhauser et collaborateurs (2005), les TCL avaient un score moyen comparativement plus bas (moyenne de 24) au MMSE et ils ont montré principalement des hypoactivations à une tâche d'attention divisée. Jusqu'à présent, une seule étude a évalué directement l'effet de la sévérité sur le patron d'activation cérébral des TCL (Celone et al., 2006). Ces auteurs ont utilisé une tâche d'encodage en mémoire épisodique chez des sujets âgés sains, des personnes TCL (divisées en deux groupes

selon leur au Cognitive Dementia Rating scale) et des patients MA. Ils ont montré que les TCL les moins atteints activaient davantage leurs hippocampes que les PA tandis que les TCL les plus atteints, tout comme d'ailleurs les patients MA, activaient moins leurs hippocampes que les PA. Ces résultats sont ainsi compatibles avec le modèle de Prvulovic et al. (2005).

1.4.1 Modèles

Jusqu'à ce jour, il n'existe aucun modèle sur la relation entre la sévérité des TCL et la nature des atteintes cérébrales. Cependant, quelques auteurs ont tenté de modéliser cette relation chez les patients MA. Un des premiers modèles proposé par Rapoport et Grady (1993) propose que dans les premiers stades de la maladie, les patients montreraient moins de métabolisme cérébral que les contrôles lors de tâches de repos ou des tâches simples, mais qu'ils auraient un niveau plus important d'activation que les contrôles lors de tâches plus exigeantes. Toutefois, une quantité plus importante de dommages neuronaux abaisserait la capacité maximale de métabolisme du cerveau des patients, ce qui occasionnerait un niveau de métabolisme inférieur à celui des contrôles dans toutes les tâches. Le modèle prédit donc la présence d'une relation sigmoïdale entre la difficulté de la tâche et les activations cérébrales, relation qui varierait selon le degré de sévérité des dommages neuronaux.

Cette approche est compatible avec des modèles plus généraux (Edelman & Gally, 2001; Friston & Price, 2003; Price & Friston, 2002) qui proposent qu'un cerveau endommagé peut, dans certaines circonstances, engager des réseaux alternatifs pour effectuer une tâche donnée. Ces modèles proposent que différents réseaux aient la

potentialité d'être réorientés vers des tâches pour lesquels ils ne sont pas spécialisés à l'origine. Cela pourrait expliquer pourquoi les personnes saines ne montrent pas tous le même patron d'activation durant la même tâche en neuroimagerie. Cependant, ce type de compensation ne serait plus possible une fois que tous les réseaux potentiels sont altérés, comme dans les stades plus avancées des maladies neurodégénératives. Ainsi, le modèle de dégénérescence propose un certain équilibre entre l'accumulation des lésions et l'habileté du système cérébral à pouvoir compenser.

L'utilisation de réseaux alternatifs comme mécanisme compensatoire a été observé à plusieurs reprises dans la littérature de neuroimagerie chez les sujets jeunes. Par exemple, Banich (1998) a démontré l'importance d'une activation bihémisphérique pour la compensation. En effet, une telle interaction entre les deux hémisphères cérébraux serait bénéfique au traitement attentionnel parce qu'il permettrait une division du travail. Suite à ces travaux, de nombreuses études de neuroimagerie ont tenté de mieux comprendre les mécanismes compensatoires dans le vieillissement normal. Un des modèles les plus influants à l'heure actuelle est le modèle HAROLD (Hemispheric Asymmetry Reduction in OLDer adults). Cette théorie soutient que les jeunes ont tendance à activer un des deux lobes préfrontaux de manière proéminente durant l'exécution de tâches cognitives (apprentissage, récupération en mémoire à long terme, mémoire de travail, fonctions exécutives et perception) tandis que les personnes âgées ont plutôt tendance à activer le cortex préfrontal de manière bilatérale, suite à la mise en place de mécanismes compensatoires. De plus, cette symétrie préfrontale serait résistante à un changement de stratégie cognitive induite expérimentalement (Logan, Sanders, Snyder, Morris, & Buckner, 2002).

Un modèle plus récent et similaire à celui de Rapoport et Grady (1993) a ramené l'idée d'une interaction entre la sévérité des dommages neuronaux, la difficulté de la tâche et le degré de performance des sujets sur les activations cérébrales dans les maladies neurodégénératives (Prvulovic et al., 2005; Wermke, Sorg, Wohlschlager, & Drzezga, 2008). Ce modèle propose que le niveau d'activation d'une structure cérébrale dépende de son efficacité à traiter l'information et de sa capacité de réserve. Ainsi, une lésion mineure diminuerait l'efficacité de la région atteinte mais pas sa capacité de réserve. Dans ce cas, la région atteinte pourrait augmenter son niveau d'activité cérébrale et ainsi compenser les effets de la lésion. Cette hyperactivation s'accroisserait avec la difficulté de la tâche jusqu'à ce qu'elle excède sa capacité maximale. Il n'y aurait alors plus de compensation possible et les performances diminueraient. En revanche, un dommage plus important diminuerait tant la capacité de réserve, que de traitement. La région atteindrait alors beaucoup plus rapidement son niveau d'activation maximale. Elle montrerait donc généralement un niveau d'activation inférieur à celui des sujets sains, sauf pour les tâches peu exigeantes. Le modèle prédit ainsi qu'une maladie évolutive devrait d'abord s'accompagner d'une hyperactivation des régions cérébrales lésées qui sont normalement requises par la tâche - reflétant un processus de compensation - puis produirait une hypoactivation des mêmes régions.

1.5 Les effets de difficulté et du type de tâche

Selon ces modèles, le degré de difficulté de la tâche pourrait expliquer des différences dans les activations. Quelques indications vont dans ce sens. Ainsi, Becker et al (1996) rapportent des activations typiques chez les personnes avec MA lors d'une

tâche de répétition de trois mots (Becker et al., 1996) alors que Woodard et al (1998) observent des hyperactivations préfrontales pour une tâche de répétition de cinq ou dix mots (Woodard et al., 1998). La répétition de listes plus courtes est vraisemblablement plus facile et mieux réussie que la répétition de listes plus longues. Le cerveau des patients MA aurait donc la capacité de recruter les réseaux nécessaires à la réalisation d'une tâche simple. Il en serait toutefois autrement pour les tâches plus exigeantes, où les ressources neuronales du réseau typique seraient insuffisantes et nécessiteraient l'activation de réseaux alternatifs.

Le type de processus cognitif sollicité par la tâche pourrait aussi contribuer à l'hétérogénéité des résultats, tout particulièrement chez les personnes TCL où le niveau d'atteinte semble différer d'un processus cognitif à l'autre. À titre d'exemple, des hyperactivations ont été observées chez les TCL lors d'une tâche de mise-à-jour où leurs performances étaient similaires à celle des personnes âgées saines (Yetkin et al., 2005) tandis que des hypoactivations ont été observées lors d'une tâche d'attention divisée où leurs performances étaient inférieures à celles des personnes âgées saines (Dannhauser et al., 2005). Cela suggère que les patients pourraient montrer des hyperactivations lors de tâches impliquant des processus cognitifs peu atteints par la maladie et des hypoactivations pour des processus cognitifs plus atteints. Il semble ainsi important de prendre en considération le degré de difficulté de la tâche et le type de processus cognitif impliqué lors de l'analyse des résultats de la littérature. Jusqu'à ce jour, aucune étude n'a évalué directement ces effets de difficulté de la tâche et du type de processus cognitif impliqué chez la population TCL.

Par ailleurs, la performance inférieure chez les patients MA par rapport à celle des sujets contrôles pourrait en partie refléter des différences au niveau de la motivation des participants et ainsi représenter une variable confondante dans les études rapportées plus haut. Afin de contrôler pour ce facteur, une étude a utilisé une tâche d'apprentissage de mots dans laquelle les performances des MA (de niveau léger à modéré) et des PA étaient utilisée comme covariable dans l'analyse des activations (Remy, Mirrashed, Campbell, & Richter, (2005). En faisant ce type de contrôle statistique, les auteurs observent que les MA hyperactivent les gyri préfrontaux moyens, supérieurs et dorsolatéraux gauches et hypoactivent le gyrus préfrontal inférieur bilatéralement, le gyrus temporal moyen droit, le cortex perirhinal gauche, le noyau cingulé postérieur gauche et le lobe pariétal bilatéralement. Ainsi, les différences d'activation entre les deux groupes semblent être le fruit de changements au niveau des circuits neuronaux. Il est à noter que ces auteurs ont observé des résultats similaires avec les TCL.

1.6 Objectifs et hypothèses

En résumé, la mémoire épisodique et la mémoire de travail sont des composantes altérées très tôt dans la MA. Les études en neuroimagerie fonctionnelle dans la MA révèlent principalement des hypoactivations au niveau des régions associées aux fonctions mnésiques ainsi que des hyperactivations au niveau du cortex préfrontal. On connaît toutefois très peu la nature des activations dans le TCL. Le TCL étant un prodrome de la MA, on pourrait s'attendre à trouver des hypoactivations dans des régions similaires à celles qui ont été rapportées dans la MA. De plus, les récents modèles de compensation cérébrale dans les maladies neurodégénératives suggèrent

des différences dans le patron d'activation en neuroimagerie en fonction de la sévérité de la maladie. Or le TCL est évolutif et ces hypothèses on été peu explorées dans cette condition. Ces différences pourraient aussi dépendre du degré de difficulté de la tâche et des processus cognitifs impliqués.

L'objectif principal de cette thèse est d'étudier les activations fonctionnelles associées à la mémoire épisodique et à la mémoire de travail dans le TCL. La thèse s'intéresse également aux effets de la sévérité de la maladie et des caractéristiques de la tâche sur les patrons d'activation cérébrale des personnes présentant un TCL. La thèse comprend cinq articles empiriques. Deux articles sont ajoutés en annexe (Annexe I et Annexe II). Ces articles portent sur des questions de recherche reliées à la thématique du TCL, mais qui ne sont pas en lien direct avec les objectifs de cette thèse.

Étude 1:

Objectifs: Le but du premier article est d'apporter un préalable méthodologique aux articles suivants puisqu'il mesure la fiabilité du signal IRMf chez les personnes TCL et chez les individus âgés sains. L'obtention d'un signal fiable est en effet indispensable à la recherche clinique en évaluant si les mesures de fMRI peuvent être utilisées pour mesurer l'effet des traitements ou comme marqueur de progression. Il s'agit donc d'une information importante pour soutenir l'utilité des études s'intéressant à la sévérité de la maladie. Des tâches d'encodage et de récupération de mots ainsi que des tâches de traitement phonologiques (c-à-d. la lecture de pseudomots) ont donc été administrées à deux reprises à 10 personnes âgées saines et à 10 personnes TCL afin de

vérifier la fidélité inter-séance du patron d'activation moyen de chaque groupe et des différences intergroupes.

Hypothèse: Je fais l'hypothèse d'une fiabilité du signal IRMf tant pour le groupe de personnes TCL que pour le groupe de personnes âgées saines. Cela devrait se manifester par des patrons d'activation relativement similaires d'une session à l'autre et par l'absence d'effet de session dans les ANCOVAs. Ainsi, les différences d'activation entre les personnes âgées saines et les TCL ne devraient pas être altérées après six semaines d'intervalle.

Étude 2:

Objectif: Le but du deuxième article est de comparer le patron d'activation cérébral des personnes âgées saines et des personnes TCL ainsi que de déterminer s'il y a un effet de sévérité sur ces différences d'activation. Pour ce faire, nous avons enregistré l'activation cérébrale de 12 personnes TCL et de 10 personnes âgées saines alors qu'elles réalisent une tâche d'encodage et de récupération de mots et de pseudo-mots. Vu le petit effectif, l'effet de la sévérité est évalué ici en corrélant l'activation au score obtenu à l'échelle Mattis Dementia Rating Scale (MDRS; Mattis, 1976) qui reflète le fonctionnement cognitif global.

Hypothèses:

- Il devrait y avoir des différences d'activation entre les personnes âgées saines et les TCL durant l'encodage et durant la récupération.

- Des différences devraient être trouvées dans les régions connues comme étant souvent compromises structurellement, ou montrant de l'hypométabolisme à la TEP, dans la MA.

- Nous nous attendons à observer une combinaison d'hyperactivation et d'hypoactivation.

- Une corrélation est attendue entre les activations observées chez les TCL et leurs scores à la MDRS, les personnes étant plus atteintes par la maladie montrant plus d'hypoactivations que les moins atteintes.

Étude 3:

Objectifs. L'article 3 évalue l'activation fonctionnelle associée à l'encodage en mémoire épisodique dans le TCL ainsi que l'impact de la sévérité de la maladie et du type d'encodage sur ces activations. L'étude rapporte les activations associées à une tâche d'encodage associatif en comparant l'encodage de paires de mots reliés sémantiquement et l'encodage de paires de mots non-reliés sémantiquement. Ces deux conditions permettent de comparer les activations associées à une condition nécessitant davantage de ressources cognitives pour mettre en relation les diverses unités d'informations (paires de mots non-reliés sémantiquement) à une condition nécessitant moins de ressources cognitives (paires de mots reliés sémantiquement). L'effet de la sévérité est évalué en utilisant la médiane du groupe de TCL au test de MDRS pour déterminer un groupe de TCL plus atteints (score inférieur à la médiane du groupe) à un groupe de TCL moins atteints (score supérieur à la médiane du groupe). Ces deux

groupes de 13 TCL chacun sont comparés à un groupe de 14 personnes âgées sans atteinte cognitive.

Hypothèses:

- Les TCL moins atteints devraient montrer principalement des hyperactivations fonctionelles, c'est-à-dire plus d'activations que les personnes âgées saines.

- Les TCL plus atteints ne devraient pas montrer d'hyperactivation. Au contraire, ils devraient montrer soit des hypoactivations, c'est-à-dire moins d'activation que les personnes âgées saines, ou un niveau d'activation similaire au groupe contrôle.

- Les hyperactivations devraient être situées soit dans des régions qui sont connues pour leur implication dans le processus cognitif évalué, soit dans des réseaux alternatifs qui pourraient être recrutés de façon compensatoires. De plus, l'emplacement de ces régions d'hyperactivation pourrait aussi dépendre du type de mécanisme compensatoire: des hyperactivations pourraient ainsi se situer dans des régions impliquées dans le traitement sémantique.

- Les hypoactivations devraient aussi être situées principalement dans des régions qui sont connues pour être atteintes dans la MA.

Étude 4:

Objectifs: L'étude 4 évalue l'activation fonctionnelle associée à la récupération en mémoire épisodique dans le TCL ainsi que l'impact de la sévérité de la maladie et du

type de processus de récupération sur ces activations. Cela est mis en évidence à l'aide d'une tâche de reconnaissance de paires de mots comprenant une condition dans laquelle les paires de mots à la récupération seront soit intactes, soit recombinées (mesure les processus de familiarité et de recollection) et une condition dans laquelle les paires seront soit intactes, soit nouvelles (mesure uniquement le processus de familiarité). Ces deux conditions permettent de comparer les activations associées à une condition nécessitant davantage de ressources cognitives en raison du caractère associatif de la tâche (paires intactes et recombinées) à une condition nécessitant moins de ressources cognitives (paires intactes et nouvelles). La médiane du groupe de TCL au test de MDRS est encore une fois utilisée pour déterminer un groupe de TCL plus atteints (score inférieur à la médiane du groupe) à un groupe de TCL moins atteints (score supérieur à la médiane du groupe), afin de déterminer l'impact de la sévérité sur le patron d'activation cérébrale. Ces deux groupes de 13 TCL chacun sont comparés à un groupe de 14 personnes âgées sans atteinte cognitive.

Hypothèses:

- Les TCL moins atteints devraient montrer principalement des hyperactivations.
- Les TCL plus atteints ne devraient pas montrer d'hyperactivations. Au contraire, ils devraient montrer soit des hypoactivations, c'est-à-dire moins d'activation que les personnes âgées saines, ou un niveau d'activation similaire au groupe contrôle.
- Les hyperactivations devraient être situées soit dans des régions qui sont connues pour leur implication dans le processus cognitif évalué, soit dans

des réseaux alternatifs qui pourraient être utilisés comme mécanismes compensatoires.

- Les hypoactivations devraient aussi être situées principalement dans des régions qui sont connues pour être atteintes dans la MA.

- Les résultats devraient dépendre du type de processus cognitif impliqué: le processus altéré le plus précocement dans la MA (ex.: recollection) devrait montrer des hyperactivations chez les MCI les moins atteints et des hypoactivations chez les MCI les plus atteints. Par ailleurs le processus cognitif altéré plus tard dans la MA (ex.: familiarité) devrait plutôt montrer des hyperactivations chez les MCI les plus atteints, car les mécanismes compensatoires ne devraient pas encore être dégradés.

Étude 5:

Objectifs: Enfin, l'étude 5 évalue le patron d'activation cérébrale associé à certaines composantes des fonctions exécutives dans le TCL ainsi que l'impact de la sévérité de la maladie et du type de processus cognitif sur ces activations. Pour ce faire, deux tâches impliquant des composantes différentes de l'administrateur central de la mémoire de travail, soit la manipulation de l'information et l'attention divisée, ont été administrées à des personnes TCL et à des personnes âgées saines. L'effet de sévérité est à nouveau étudié par l'entremise des résultats au test de MDRS où la médiane du groupe de TCL a été utilisée pour déterminer un groupe de TCL plus atteints (score inférieur à la médiane du groupe) à un groupe de TCL moins atteints

(score supérieur à la médiane du groupe). Ces deux groupes de 12 TCL chacun sont comparés à un groupe de 14 personnes âgées sans atteinte cognitive.

Hypothèses:

- Les TCL moins atteints devraient montrer principalement des hyperactivations, c'est-à-dire plus d'activations que les personnes âgées saines.

- Les TCL plus atteints ne devraient pas montrer d'hyperactivations. Au contraire, ils devraient montrer soit des hypoactivations, c'est-à-dire moins d'activation que les personnes âgées saines, ou un niveau d'activation similaire au groupe contrôle.

- Les hyperactivations devraient être situées soit dans des régions qui sont connues pour leur implication dans le processus cognitif évalué, soit dans des réseaux alternatifs qui pourraient être utilisés comme mécanismes compensatoires.

- Les hypoactivations devraient aussi être situées principalement dans des régions qui sont connues pour être atteintes dans la MA.

CHAPITRE 2

Article n° 1

Test-retest reliability of fMRI verbal episodic memory paradigms in healthy older adults and in persons with mild cognitive impairment

Francis Clément & Sylvie Belleville

Human Brain Mapping 2009; 30 : 4033-4047.

Abstract

This study investigated test–retest fMRI reproducibility in 10 healthy older adults and in 10 MCI persons using a two-condition (encoding and retrieval) verbal episodic memory task as well as a two-condition (with and without a motor response) phonological processing task. Reproducibility measures included an overlap ratio with four different thresholds, statistical comparisons of the condition contrasts across sessions (test-retest contrasts), ANCOVAs and intraclass correlation (ICC) on selected regions of interests (ROIs). In all four conditions and for all reproducibility measures, MCI individuals showed fMRI test-retest reproducibility indices that were comparable to those of healthy older adults. At the group level, the comparison of the test-retest condition contrasts yielded very few differences in the areas and level of activation and those differences tended to show a slight reduction of activation in the second session. In addition, the results from the ANCOVAs showed that the fMRI signal measured at the group level does not vary significantly from one session to another. Overlap ratios however showed that the fMRI signal failed to produce a reliable pattern of significantly activated voxels across sessions. At the individual level, ICC analyses on selected ROIs indicated that there is high within-subject variability, suggesting reduced reliability at the individual level. Overall, these findings indicate that MCI individuals show fMRI test-retest reproducibility comparable to those healthy controls and hence that mild cognitive impairment do not alter fMRI reproducibility. Furthermore, they indicate that monitoring treatment effects is reliable when comparing groups but reduced when comparing single individuals. These results have precise implications for the design of longitudinal studies relying on fMRI measures in older adults.

Introduction

There is increasing interest in the use of functional magnetic resonance imaging (fMRI) as a diagnostic tool for age-associated cognitive disorders. This technique also yields considerable interest as a potential marker for therapeutic treatment of age-related neurodegenerative diseases, such as Alzheimer's disease (AD) or mild cognitive impairment (MCI).

People with mild cognitive impairment (MCI) show greater cognitive decline than expected relative to people of the same age and education level. Indeed, MCI has been identified as a risk factor for the development of AD as it has been shown that a large proportion of persons who meet the clinical criteria for MCI will progress to dementia (Gauthier et al., 2006). No cure has yet been found for AD, though a number of studies have investigated the possibility of pharmaceutical (e.g.: Gron, et al. 2006; Saykin, et al. 2004) and non-pharmaceutical interventions (e.g.: Ball, et al. 2002; Belleville, et al. 2006; Craik, et al. 2007; Rapp, et al. 2002) to enhance mnesic abilities in healthy older adults and in persons with MCI or to at least slow the initial rate of progression toward AD (Petersen and Morris 2005). With the advancement of neuroimaging technologies, it is now possible to quantify cognitive decline and the effects of a given intervention in terms of changes in cerebral activation, in addition to characterizing modifications in behaviour (e.g.: Goekoop, et al. 2004; Goekoop, et al. 2006; Gron, et al. 2006; Saykin, et al. 2004). Neuroimaging techniques could become useful clinical tools for quantifying longitudinal cerebral activation changes associated with a disease or intervention effects. However, the use of fMRI in clinical and research studies that involve repeated measures requires firm evidence that measures of brain

activation in those populations are reliable indicators and do not vary in test-retest measurements. More precisely, it is crucial to know whether or not the fMRI signal is reproducible, i.e. if two functional magnetic resonance imaging (fMRI) sessions produce comparable activations.

The vast majority of fMRI reliability studies have been performed on young healthy subjects performing a variety of cognitive and noncognitive tasks, including sensory tasks (Kiehl and Liddle, 2003; Miki et al., 2000; Rombouts et al., 1998; Rombouts et al., 1997; Specht et al., 2003; Stark et al., 2004; Waldvogel et al., 2000; Yetkin et al., 1996), motor tasks (Havel et al., 2006; Liu et al., 2004; Loubinoux et al., 2001; Raemaekers et al., 2007; Swallow et al., 2003; Waldvogel et al., 2000; Yetkin et al., 1996), memory tasks (Machielsen et al., 2000; Miller et al., 2002; Wagner et al., 2005), executive function tasks (Aron et al., 2006; Neumann et al., 2003; Wei et al., 2004), and language tasks (Maldjian et al., 2002; Rutten et al., 2002). These studies generally report a reasonably good, though not perfect, reproducibility of fMRI cerebral activations.

While there is no general consensus as to the appropriate method that should be used to assess fMRI reproducibility across sessions, many studies (Fernandez et al., 2003; Havel et al., 2006; Machielsen et al., 2000; Miki et al., 2000; Raemaekers et al., 2007; Rutten et al., 2002; Specht et al., 2003; Swallow et al., 2003; Wagner et al., 2005; Yetkin et al., 1996) have used the overlap ratio initially used by Rombouts et al. (1997) which measures reproducibility in the number and location of voxels by comparing voxels activated in both sessions to those activated in only one of them. Overall, the

overlap ratio does not vary widely though there is some task related effect with higher overlap ratios found when using sensorimotor tasks (ex.: from 0.48; Miki, et al. 2000, to 0.64; Rombouts, et al. 1998) relative to higher level cognitive tasks (ex.: from 0.36; Machielsen et al., 2000; Wagner et al., 2005 to 0.42; Wagner, et al. 2005, in the case of memory tasks). Another fMRI reproducibility method that has been used by many researchers is the intraclass correlation (ICC) (Aron, Gluck, & Poldrack, 2006; Fernandez et al., 2003; Kong et al., 2007; Manoach et al., 2001; Raemaekers et al., 2007; Specht, Willmes, Shah, & Jancke, 2003; Wei et al., 2004). ICC assesses fMRI activation reliability by comparing the between-subject variance to total variance and it is therefore higher when within-subject variance is low and between-subject variance is high. In healthy subjects, the ICC seems to vary greatly from one study to another and from one region to another.

Reliance on repeated scans is likely to be particularly vital in clinical populations as researchers are attempting to elucidate the brain-related effects of disease evolution and/or of treatment. Nevertheless, the reproducibility of fMRI signal in patients has not been extensively studied and thus remains largely unknown. We are aware of only four studies conducted on different clinical populations: schizophrenic patients (Manoach, et al. 2001), stroke patients (Chen and Small 2007), patients with focal epilepsy (Fernandez, et al. 2003), and patients with chronic nonfluent aphasia (Kurland et al., 2004). The results of these studies suggest that patients show less reliable activations across sessions than healthy participants, possibly due to unstable brain compensation, greater head movement than controls, and more variability in task performances. However, all of these patients suffered from chronic symptoms, hence it is difficult to transpose these

results to a population with a slowly evolving disease; furthermore, very little is known about the impact of aging on fMRI reproducibility. Indeed, only one study assessed fMRI reproducibility in healthy older adults using an N-Back working memory task and a finger-tapping task (Marshall, et al. 2004). These studies concluded that across-session fMRI reproducibility in older adults is similar to the one reported in young subjects. More studies are required in order to extend these findings to other cognitive functions in elderly people and to know whether these results also apply to MCI individuals.

The goal of this study was to assess the reproducibility of fMRI signal in healthy older adults and in MCI persons with a verbal memory task, a cognitive task typically used as a diagnostic marker of dementia, with both an encoding and a retrieval condition. A phonological processing task was also used. This is a task that is typically unimpaired in MCI and early AD that can provide indications regarding reproducibility values in unimpaired conditions. Two conditions were also used in the phonological task: one that included a motor response and one that did not include a motor response because memory conditions also included either a motor response (in the retrieval condition) or no motor response (in the encoding condition). This allowed us to assess the relative contribution of the motor response component to the overlap ratio of the memory and phonological tasks. These paradigms were used because, as mentioned earlier, tasks with a motor response tend to produce higher overlap ratios than tasks with no motor component. It was therefore important to ensure that task differences in reproducibility were not related to the motor component. Reproducibility was assessed in each group using the overlap ratio measure, statistical comparisons of the condition contrasts across sessions, as well as ICC measure and statistical comparison of the beta values in selected

Regions-of-Interest (ROI) that are known to be involved in verbal memory and/or phonological processing (Cabeza & Nyberg, 2000): Broca's area (BA 44), the left and right ventrolateral prefrontal cortex (BA 45, 47), the left and right dorsolateral prefrontal cortex (BA 9, 46), the precuneus bilaterally, the posterior cingulate cortex bilaterally, and in the hippocampus bilaterally. As the overlap ratio method can be threshold sensitive, overlap ratio measures were done using four different threshold values. We first hypothesized that healthy older adults and MCI persons would both show relatively good fMRI reproducibility of a similar magnitude as those observed in the literature with younger adults; moreover, we also hypothesized that conditions that included a motor response would show a higher overlap ratio than conditions that did not include a motor response, due to the higher fMRI reproducibility of sensorimotor cortices. Lastly, we predicted that the statistical comparisons of the condition contrasts across sessions would highlight a reduction of activation in some areas from the first to the second session, in accordance with the literature (see Kelly and Garavan 2005).

Method

Participants

A total of 20 participants, 10 MCI persons and 10 healthy older adults participated in this study. Persons with MCI (3 males) had a mean age of 67.20 years (SD = 8.03, median = 73, range = 51-74) and had a mean of 13.7 (SD = 3.8, median = 11.5, range = 9-18) years of education. Healthy older adults (2 males) had a mean age of 71.20 years (SD = 7.25, median = 69, range = 58-80), with an average of 12.90 (SD = 2.5, median = 13, range = 8-20) years of education. French was the first language of all participants.

Participants with MCI were recruited from memory clinics and met the criteria proposed by Petersen et al (1999) for amnestic single or multiple domain MCI: 1) they had a memory complaint; 2) they performed at least 1.5 SD below the average level of persons of similar age and education on standardized memory tests; 3) they showed no global cognitive impairment on the basis of the MMSE (using the age- and education-adjusted cutoff for dementia); 4) nor any significant impact on daily functions as measured by the SMAF functional impairment scale and clinical interview; 5) they failed to meet criteria for dementia. MCI participants went through an extensive neuropsychological evaluation that covered episodic memory (a cued and free word recall task: RL/RI-16; Buschke 1984; Van der Linden, et al. 2004, a text memory of the BEM; Signoret 1991, and the recall of Rey's Complex Figure; Rey 1959), executive functions (third set of Victoria Stroop; Regard 1981, and copy of Rey's Complex Figure; Rey 1959), visuospatial processing (Benton Judgment of line orientation; Benton, et al. 1983), information processing speed (Coding of the WAIS-III; Wechsler 1997), language (Boston Naming Test; Kaplan, et al. 1983), and global cognitive functions (Mattis Dementia Rating Scale, MDRS; Mattis 1976, and Mini-Mental State Examination, MMSE; Folstein, et al. 1975). In addition, depressive symptoms were assessed with the Geriatric Depression Scale (GDS; Yesavage 1988) and vascular risk factors were assessed with the Hachinski questionnaire (Hachinski, et al. 1975). MCI persons also went through an extensive medical, neurological and neuroradiological examination to exclude the presence of any significant systemic, neurological or psychiatric condition that could explain their cognitive difficulties.

Elderly controls were recruited from the community. They also completed a clinical and a partial neuropsychological assessment (MDRS, MMSE, MOCA, GDS, RL/RI-16) to ensure that they did not suffer from cognitive deficits. Exclusion criteria included past history of psychiatric or neurological disorders, including traumatic brain injury and depression. This study was approved by the Institut Universitaire de Gériatrie de Montréal Human Ethics Committee and was part of a larger intervention study as a control condition.

Stimuli

Six lists of eight concrete, one- to three-syllable words were created for the learning phase of the memory task. The six lists were matched in terms of mean word frequency, semantic category and concreteness of the words in the list. Six lists of eight concrete, one- to three-syllable words were created for the retrieval phase. Half of the words used in the retrieval lists were part of the encoding list and half were new words. The new words were matched to the old words in terms of the relevant linguistic dimensions (syllabic length, frequency, and concreteness).

Twelve lists of six pseudo words were created for the phonological processing task. Six were used in the motor response condition and six were used in the no-response condition. The pseudo words were matched to the words used in the memory task in terms of the relevant linguistic dimensions (length, phonological complexity, and frequency of the words from which they were derived).

Two parallel versions of the memory lists were used in this study and were counterbalanced across subjects so that each list was presented to equivalent number of participants on each session.

Neuroimaging procedure

The task was programmed on E-prime and stimuli were visually presented and mirror-projected. Subjects' vision was corrected with goggles appropriate for MRI scanning. During rest, subjects were instructed to close their eyes and to try not to think about anything. During phonological processing without a motor response, subjects were instructed to read covertly a series of pseudo words. During phonological processing with a motor response, subjects were instructed to read covertly a series of pseudo words and to press randomly using a two-button response. Each phonological processing block or series contained six pseudo words (4 sec presentation rate, 1 sec interstimulus interval). There were six blocks for a total of 36 pseudo words. During memory encoding, subjects were asked to memorize series of visually presented words. Each encoding block or series contained eight words (4 sec presentation rate, 1 sec interstimulus interval). There were six encoding blocks for a total of 48 words. During memory retrieval, subjects were asked to perform an old-new recognition judgment of visually presented words using a two-button response. Each retrieval block or series contained eight words (4 sec presentation rate, 1 sec interstimulus interval), half of which were presented in the preceding encoding blocks, half of which were new. There were six retrieval blocks for a total of 48 words.

Subjects performed the task in a blocked design with one encoding run and one retrieval run. The encoding run was composed of six alternating blocks series of rest, phonological processing without a motor response, and intentional encoding (i.e. six series of: rest, <task1>, <task2>) with each session lasting 28 sec, 30 sec, and 40 sec, respectively. In addition, a brief instruction (4 sec) was presented to the subjects prior to each block. A retrieval run composed of six alternating block series of rest, phonological processing with a motor response, and retrieval followed by the encoding run. The rest, phonological processing with a motor response, and retrieval blocks lasted 28 sec, 30 sec, and 40 sec, respectively, and were preceded by instructions. Two days prior to scanning and just before the scanning session, subjects were trained using an fMRI simulator. The whole procedure was repeated again 6-weeks later.

Data acquisition

Magnetic Resonance Imaging (MRI) was performed using a SIEMENS 3T Magnetom TRIO a TIM System (Erlangen, Germany) at the Unité de Neuroimagerie Fonctionnelle (UNF) of the Institut Universitaire de Gériatrie de Montréal. Functional MR images were acquired using Gradient-Echo Echo-Planar imaging sequences (GE-EPI) sensitive to blood oxygen level-dependent (BOLD) contrast (TR/TE = 2000/30 ms, flip angle = 90 deg; 31 interleaved slices, voxel size = 3.75 mm x 3.75 mm x 5 mm with a gap of 1 mm, field of view = 240 mm, matrix = 64*64). A 3-D structural image was taken at the end of the two runs using a sagittal T1-weighted 3D-MPRAGE sequence was obtained (TR/TE = 1950/3.93 ms, flip angle = 15 deg; 176 slices, voxel size = 1 mm x 1 mm x 1 mm, field of view = 256 mm, matrix = 256*256).

Image processing and data analysis

Data were analyzed in MATLAB 7.0 (http://www.mathworks.com) using the statistical parametric mapping software SPM2 (http://www.fil.ion.ucl.ac.uk/spm/). The first three volumes were automatically discarded by the fMRI scanner in order to allow the magnetization to reach equilibrium. The remaining functional images were first converted into Analyze format and unwarped. Functional volumes of each subject were then realigned to the first acquired volume in the session and a mean realigned volume was created for each subject. All the realigned volumes of each subject were spatially normalized into the Montreal Neurological Institute (MNI) stereotactic space and spatially smoothed with an 8-mm Gaussian kernel. Low-frequency noise was removed with a high-pass filter of 256 sec. Global changes in fMRI response from scan to scan were removed by proportionally scaling each volume to a common global mean voxel value. A single-subject analysis was carried out in order to evaluate the individual contrasts (encoding vs. rest, retrieval vs. rest, phonological processing without a motor response vs. rest, and phonological processing with a motor response vs. rest) for each subject. The instruction blocks were modeled as a condition of no-interest. A Random Effects (RFX) Analysis was then performed by calculating, for each group (healthy older adults and MCI), a one way ANOVA with 8 conditions (encoding session 1, encoding session 2, retrieval session 1, retrieval session 2, phonological processing without a motor response session 1, phonological processing without a motor response session 2, phonological processing with a motor response session 1, phonological processing with a motor response session 2), with non-sphericity correction, replications over subjects, and with correlated repeated measures. In order to visualize the area of overlapping volume

for each group, an inclusive mask of the first and second measurement of encoding, retrieval, and phonological processing with and without a motor response was performed. This analysis has been used previously to assess the reliability of a verbal episodic memory task in young adults (Wagner, et al. 2005). An uncorrected threshold of $p<0.001$ with 10 contiguous voxels was used for both the overlap ratio and the test-retest comparison. The overlap ratio method was also recalculated with uncorrected thresholds of $p<0.005$, of $p<0.0001$, and of $p<0.00001$, all with 10 contiguous voxels.

Test-retest reliability measures

Overlap ratio. The relative amount of overlapping volume $R^{ij}_{overlap}$ between two activation SPM maps was calculated according to a method introduced by Rombouts et al. (1997) based on Dice coefficient (D) (Dice, 1945):

$$R^{ij}_{overlap} = \frac{2*V_{overlap}}{V_i + V_j}$$

where V_i = number of suprathreshold voxels within SPM(*t*) maps in session i, V_j = number of suprathreshold voxels within SPM(*t*) maps in session j, and $V_{overlap}$ = the number of suprathreshold voxels in both maps. The overlap ratio can range from 0 to 1 and is based strictly on the location of significantly activated voxels and not on the actual *t* values of these voxels. Overlap ratios were also converted to Jaccard coefficients (J), which are the ratio of the size of the intersection divided by the size of the union of activated voxels:

$$J(S_1, S_2) = \frac{|S_1 \cap S_2|}{|S_1 \cup S_2|}$$

where S_1 represents the activated voxels of the first fMRI session and S_2 represent the activated voxels of the second fMRI session. The Jaccard coefficient has been used in structural imaging for tissue classification (Shattuck, Sandor-Leahy, Schaper, Rottenberg, & Leahy, 2001) but has not, to our knowledge, been used yet as an index of reliability for functional neuroimaging. The conversion from the overlap ratio (or more precisely from the Dice coefficient) can be performed with the following formula:

$$D = \frac{2J}{(1+J)}$$

Or:

$$J = \frac{-D}{D-2}$$

In contrast to the overlap ratio, the Jaccard coefficient can be directly interpreted as the percentage of the voxels that are activated during both sessions (ex: J = 0.21 = 21% of the voxels activated during both sessions).

Test-retest comparison. One limitation of the overlap ratio is that thresholding an image can exaggerate very small differences and hence lead to considerable differences in the size of the overlap ratio obtained. For instance, a voxel can show very similar signal strength during two sessions but with one signal being slightly below the threshold and the other one being slightly above. The calculation of the overlap ratio would consider this voxel as being inconsistent from one session to another, despite the fact that its signal strength was similar. For this reason, we also compared the SPM(*t*) encoding,

retrieval, and phonological processing with and without motor response contrasts of both sessions.

Beta values comparisons and ICCs in ROIs. A ROI image of Broca's area (area 44), of the left and right ventrolateral prefrontal cortex (BA 45, 47), of the left and right dorsolateral prefrontal cortex (BA 9, 46), of the precuneus bilaterally (BA 7), of the posterior cingulate cortex bilaterally, and of the hippocampus bilaterally were created with WFU Pickatlas (Maldjian, et al. 2003). Then, the average beta values of the ROIs were extracted with marsbar (Brett, et al. 2002) for each group and for each condition during both sessions. Three-way mixed ANCOVAs with Group (controls, MCI) as a between-subject factor, Session (1, 2) and Condition (encoding, retrieval, phonological processing without a motor response, and phonological processing with a motor response) as within-subject factors, and Age and Education as covariates were performed in SPSS 13.0 (http://www.spss.com) to assess possible group differences as well as reliability of the beta values from session 1 to session 2. Shrout-Fleiss two-way single measure absolute agreement random ICC model (2,1) were also performed on the average beta values of each ROIs for each subject and for each session. The unit of observation was the subject. F-tests reference test-value was set to 0 with a confidence interval of 95%. The ICC analyses were also performed in SPSS 13.0.

Results

Sociodemographic data

To assess whether the groups differed on age and education, two t-tests were performed on these two variables. No significant age, $t(18) = 1.38$, N.S., or education

effect, t(18) = -0.88, N.S., were found. This indicates that the control group was age- and education-matched to the MCI group.

Neuropsychological evaluation

Independent t-tests were also performed on the neuropsychological evaluation scores obtained by the two groups. MCI participants obtained significantly lower scores than healthy controls on the MDRS, $t(18) = 2.48$, $p < 0.05$, MMSE, $t(18) = 2.63$, $p < 0.05$, 3rd free recall of the RL/RI-16, $t(18) = 2.71$, $p < 0.05$, and on the delayed recall of the RL/RI-16, $t(18) = 3.41$, $p < 0.01$ (Table I).

Behavioral data

The mean percentage of correctly recognized words was 72.07% (SD = 10.95) in the first session and 76.88% (SD = 10.24) in the second session for the control group and 67.20% (SD = 11.92) in the first session and 71.63% (SD = 12.04) in the second session for the MCI group.[1] A two-way mixed ANOVA with Group (controls, MCI) as a between-subject factor and Session (1, 2) as a within-subject factor was performed to assess whether task performances were equivalent across groups and sessions. No significant Group effect, $F(1,16) = 1.11$, N.S., Session effect, $F(1,16) = 4.09$, N.S., or Group by Session interaction, $F(1,16) = 0.01$, N.S, were found. Therefore, the two groups performed at a similar level during the two sessions and there was no behaviorally evident training effect.

[1] Note that performances of two MCI persons were not recorded due to equipment difficulties.

Neuroimaging data and test-retest comparisons

Memory encoding. The activations for the memory encoding condition for sessions 1 and 2 of the healthy controls group (a and b respectively) and of the MCI group (c and d respectively) are shown in Figure 1. Overall, healthy controls showed activations in a frontotemporoparietal network commonly observed in episodic memory task (medial temporal lobe, anterior and posterior cingulate gyrus, precuneus, supramarginal and angular gyri, medial prefrontal cortex, and premotor areas) as well as in the occipital lobe, in subcortical structures (basal ganglia and thalamus), and in the right cerebellum. The MCI group activated the same frontotemporoparietal network during both sessions, but also showed additional activations in the prefrontal cortex (inferior prefrontal gyrus, dorsolateral prefrontal cortex and orbitofrontal regions). Statistical comparison of the two sessions for each group yielded few results as is illustrated in Table II: healthy controls showed more activation in the putamen and in the left inferior and middle temporal gyri (Brodmann's area 21) in the first session than in the second session and MCI persons showed more activation during the first session than during the second session in the left middle frontal gyrus (Brodmann's area 11). The results of the first session are described in more details elsewhere (Clement, Belleville, & Mellah, submitted).

Memory retrieval. The activations for the retrieval condition for sessions 1 and 2 of the healthy controls group (a and b respectively) and of the MCI group (c and d respectively) are shown in Figure 2. Both groups activated a similar frontotemporoparietal network as in encoding. The test-retest comparison showed no significance session effect on retrieval activations.

Phonological processing without a motor response. The activations for the phonological processing without a motor response condition for sessions 1 and 2 of the healthy controls group (a and b respectively) and of the MCI group (c and d respectively) are shown in Figure 3. During the first session, the healthy controls group showed activations in the left parahippocampal gyrus, posterior cingulate gyrus, in the occipital lobe, in the parietal lobe (precuneus and supramarginal gyrus), in the premotor area, in the thalamus, and in the cerebellum. Healthy controls showed less activation in the left putamen during the second session than during the first session. Again, the MCI group showed the same activations as controls in both sessions but with additional activations in the prefrontal cortex (in the inferior prefrontal gyrus, in the dorsolateral prefrontal cortex, and in the premotor region). The test-retest comparison for both groups indicated that healthy controls showed more activation in the left putamen during the first session than during the second session (Table III).

Phonological processing with a motor response. The activations for the phonological processing with a motor response condition for sessions 1 and 2 of the healthy controls group (a and b respectively) and of the MCI group (c and d respectively) are shown in Figure 4. During the first session, the healthy controls group showed activations in the anterior and posterior cingulate gyrus, in the occipital lobe, in the parietal lobe (precuneus, postcentral gyrus, inferior and superior parietal lobules), in the premotor area, and in the cerebellum. Healthy controls showed the same activations during the second session, with the exception of the premotor area that does not activate. Again, the MCI group showed the same activations as controls in both sessions but with

additional activations in the prefrontal cortex (in the inferior prefrontal gyrus, in the dorsolateral prefrontal cortex, and in the premotor region). A comparison between both sessions in MCI persons also indicates that they show more activation in the left cerebellum during the first session than during the second session (Table IV).

Test-retest overlap of activations

The overlap ratio was first calculated using an uncorrected threshold of $p<0.001$. In the memory encoding condition, the overlap ratio ($R_{overlap}$) in healthy controls and MCI were 0.41 (J = 0.26) and 0.40 (J = 0.25) respectively. In the memory retrieval condition, healthy controls and MCI obtained overall ratios of 0.69 (J = 0.53) and 0.70 (J = 0.54) respectively. In the phonological processing condition without a motor response, healthy controls and MCI obtained overall ratios of 0.46 (J = 0.30) and 0.42 (J = 0.27) respectively. In the phonological processing condition with a motor response, healthy controls and MCI obtained an overlap ratio of 0.68 (J = 0.52) and 0.66 (J = 0.49) respectively. Therefore, the overlap ratio was almost identical across groups and was higher in the two conditions in which a motor response was included.

The overlap ratio was recalculated using a more liberal uncorrected threshold of $p<0.005$. In the memory encoding condition, the overlap ratio ($R_{overlap}$) in healthy controls and MCI were 0.39 (J = 0.24) and 0.47 (J = 0.31) respectively, thus quite similar to the values found with a threshold of $p<0.001$. In the memory retrieval condition, healthy controls and MCI obtained overall ratios of 0.71 (J = 0.56) and 0.75 (J = 0.59) respectively, again very similar to the values mentioned above. In the phonological processing condition without a motor response, healthy controls and MCI obtained

overall ratios of 0.45 (J = 0.29) and 0.49 (J = 0.33), respectively. In the phonological processing condition with a motor response, healthy controls and MCI obtained an overlap ratio of 0.71 (J = 0.55) and 0.70 (J = 0.54), respectively. Therefore, the use of a more liberal threshold had only a slight effect on the overlap ratios in both groups.

The overlap ratio was also recalculated using two more conservative uncorrected threshold of $p<0.0001$ and $p<0.00001$. For the threshold of $p<0.0001$, in the memory encoding condition, the overlap ratio ($R_{overlap}$) in healthy controls and MCI were 0.46 (J = 0.30) and 0.25 (J = 0.14) respectively. In the memory retrieval condition, healthy controls and MCI obtained overall ratios of 0.60 (J = 0.43) and 0.64 (J = 0.47) respectively. In the phonological processing condition without a motor response, healthy controls and MCI obtained overall ratios of 0.53 (J = 0.36) and 0.32 (J = 0.19) respectively. In the phonological processing condition with a motor response, healthy controls and MCI obtained an overlap ratio of 0.59 (J = 0.42) and 0.56 (J = 0.39) respectively. For the threshold of $p<0.00001$, in the memory encoding condition, the overlap ratio ($R_{overlap}$) in healthy controls and MCI were 0.42 (J = 0.27) and 0.10 (J = 0.05) respectively. In the memory retrieval condition, healthy controls and MCI obtained overall ratios of 0.43 (J = 0.28) and 0.52 (J = 0.35) respectively. In the phonological processing condition without a motor response, healthy controls and MCI obtained overall ratios of 0.46 (J = 0.30) and 0.19 (J = 0.11) respectively. In the phonological processing condition with a motor response, healthy controls and MCI obtained an overlap ratio of 0.44 (J = 0.28) and 0.45 (J = 0.29) respectively. For all four conditions, the use of more conservative thresholds therefore reduced considerably the overlap ratios of the two groups.

Beta values comparisons in ROIs

Beta value changes from session 1 to session 2 were assessed for Broca's area (BA 44), for the left and right ventrolateral prefrontal cortex (BA 45, 47), for the left and right dorsolateral prefrontal cortex (BA 9, 46), for the precuneus bilaterally (BA 7), for the posterior cingulate cortex bilaterally, and for the hippocampus bilaterally for both groups and for the 4 conditions. Three-way mixed ANCOVA with Group (controls, MCI) as a between-subject factor, Session (1, 2) and Condition (encoding, retrieval, phonological processing without a motor response, and phonological processing with a motor response) as within-subject factors, and Age and Education as covariates were performed to assess possible group differences and reliability of the beta values from session 1 to session 2. For Broca's area (BA 44), a significant Group effect was found, $F(1,16) = 15.57$, $p < 0.001$, but no Session effect, $F(1,16) = 2.25$, N.S., or Condition effect, $F(3,48) = 1.64$, N.S., were found and no significant interaction was observed (see Figure 5). For the left ventrolateral prefrontal cortex (BA 45, 47), no significant Group effect, $F(1,16) = 1.12$, N.S., Session effect, $F(1,16) = 0.54$, N.S., or Condition effect, $F(3,48) = 1.82$, N.S. were found and no significant interaction was observed. For the right ventrolateral prefrontal cortex (BA 45, 47), no significant Group effect, $F(1,16) = 0.43$, N.S., Session effect, $F(1,16) = 0.76$, N.S., or Condition effect, $F(3,48) = 1.44$, N.S. were found and no significant interaction was observed. For the left dorsolateral prefrontal cortex (BA 9, 46), no significant Group effect, $F(1,16) = 0.05$, N.S., Session effect, $F(1,16) = 0.09$, N.S., or Condition effect, $F(3,48) = 1.19$, N.S. were found but a Group X Condition interactions was observed, $F(3,48) = 3.04$, $p < 0.05$. Post-hoc analysis showed that MCI showed significantly more activation in this ROI during the

phonological processing without a motor response condition, $p < 0.05$. For the right dorsolateral prefrontal cortex (BA 9, 46), a significant Group effect was found, $F(1,16) = 7.60$, $p = 0.01$ but no Session effect, $F(1,16) = 2.79$, N.S., or Condition effect, $F(3,48) = 0.88$, N.S. were found and no significant interaction was observed. For the precuneus bilaterally (BA 7), no significant Group effect, $F(1,16) = 0.26$, N.S., Session effect, $F(1,16) = 1.28$, N.S., or Condition effect, $F(3,48) = 1.36$, N.S. were found and no significant interaction was observed, $F(3,48) = 3.04$, $p < 0.05$. For the posterior cingulate bilaterally, no significant Group effect, $F(1,16) = 0.34$, N.S., Session effect, $F(1,16) = 0.17$, N.S., or Condition effect, $F(3,48) = 0.39$, N.S. were found and no significant interaction was observed. For the hippocampus bilaterally, no significant Group effect, $F(1,16) = 1.33$, N.S., Session effect, $F(1,16) = 0.41$, N.S., or Condition effect, $F(3,48) = 0.33$, N.S. were found. A significant Condition X Session interaction was observed, $F(3,48) = 3.81$, $p < 0.05$. Post-hoc analysis showed a significant reduction from session 1 to session 2 was observed during the phonological processing with a motor response condition, $p < 0.05$.

In summary, MCI showed significantly more activation than healthy controls in the Broca's area and in the right dorsolateral prefrontal cortex during all four conditions and more activation than healthy controls in the left dorsolateral prefrontal cortex during the phonological processing without a motor response condition only. The only significant change of activation from one session to another was observed in the hippocampus bilaterally with a reduction from session 1 to session 2 during the phonological processing with a motor response condition. No ROI showed more change

in activation from one session to another in the MCI group than in the healthy controls group.

ICC in ROIs

Single measure ICC of sessions 1 and 2 were assessed for Broca's area (BA 44), for the left and right ventrolateral prefrontal cortex (BA 45, 47), for the left and right dorsolateral prefrontal cortex (BA 9, 46), for the precuneus bilaterally (BA 7), for the posterior cingulate cortex bilaterally, and for the hippocampus bilaterally for both groups and for the 4 conditions (Table V). Healthy controls showed significant ICC in the precuneus bilaterally during the retrieval and phonological processing without a motor response conditions, in the left dorsolateral prefrontal cortex (BA 9,46) during the encoding, retrieval, and phonological processing with motor response conditions, in the left ventrolateral prefrontal cortex (BA 45, 47) during the retrieval condition, in the right ventrolateral prefrontal cortex (BA 45, 47) during the retrieval and phonological processing with motor response conditions, and in the posterior cingulate cortex during the retrieval and phonological processing with motor response conditions. MCI participants showed significant ICC in Broca's area (BA 44) during the retrieval condition, in the precuneus bilaterally during all four conditions, in the hippocampus bilaterally during the retrieval and phonological processing with a motor response conditions, in the right dorsolateral prefrontal cortex (BA 9, 46) during the retrieval, phonological processing without a motor response, and phonological processing with a motor response conditions, and in the posterior cingulate cortex during the retrieval, phonological processing without a motor response, and phonological processing with a motor response conditions. The mean ICC of healthy controls was 0.31 and the one of

MCIs was 0.36. A t-test between the ICCs of the two groups did not reveal a significant difference, $t(62) = -0.68$, N.S.

Discussion

The goal of this study was to assess the reliability of fMRI signal in healthy older adults and in MCI persons. This was done with a verbal memory task and a phonological processing task, both with and without a motor response. Although MCI persons and healthy older adults showed differences in the localization of their activations between the two sessions, a statistical comparison of session 1 and 2 revealed few significant differences even with the use of a relatively liberal threshold value ($p<0.001$). Small clusters in the putamen and in the left inferior and middle temporal lobe of the healthy older adults and in the left middle frontal gyrus of the MCI group showed less activation at Session 2 relative to Session 1. Reduction of activation during the second session is consistent with what is usually observed in studies of practice effects (see Kelly and Garavan 2005) and the changes observed in the current study likely reflect the same phenomenon. Importantly, we did not find significant behavioral performance differences between the two groups or between the two sessions. This is important for fMRI data as differences in performance could otherwise be attributed to motivational or attentional factors that might have had an impact on brain activation thus limiting the interpretation of activation differences as they relate to reproducibility.

FMRI reproducibility was also assessed by comparing the average beta values of selected ROIs in areas that that are known to be involved in verbal memory and/or phonological processing (Cabeza & Nyberg, 2000). While some group differences were observed (i.e. more activation in MCI than in healthy controls in the Broca's area and in

the right dorsolateral prefrontal cortex during all four conditions and in the left dorsolateral prefrontal cortex during the phonological processing without a motor response condition only), these group differences appear to be stable in time as no Group X Session interaction was found. Furthermore, only the hippocampus ROI showed change in activation from one session to another and this was only during one among four conditions. The comparison of beta values in the ROIs therefore suggests that the two groups show reliable session-to-session fMRI signal, at least in the regions investigated in this study. Overall, these results, combined with the statistical comparisons of Sessions 1 and 2, suggest that in older adults with or without cognitive decline, the fMRI signal elicited by the execution of the four conditions used here do not vary significantly when measured in two sessions that are six weeks apart.

The test-retest reliability was also assessed with the overlap ratio, a commonly used reliability method that measures reproducibility by comparing number and location of voxels activated in both sessions compared to those activated in only one of them. The group overlap ratios ($R_{overlap}$) of healthy controls and of MCI were almost identical in the four conditions with an uncorrected threshold of $p<0.001$ and were very similar when using an uncorrected threshold of $p<0.005$. This was the case whether tested with a relatively simple phonological task or with a more demanding memory task irrespective of the motor response. For these two thresholds, the encoding overlap ratio of both groups is very close to the one previously reported in healthy young adults (0.41 in healthy older adults and 0.40 in MCI respectively, vs. 0.36 in healthy young adults; Machielsen, et al. 2000; Wagner, et al. 2005) and the overlap ratio associated with retrieval is higher in both groups than that previously reported in healthy young adults

(0.69 in healthy older adults and 0.70 in MCI, vs. 0.42 in healthy young adults; Wagner, et al. 2005). Thus the present data indicate that MCI persons show overlap ratios that are comparable to those found in healthy older adults and healthy young adults and that this overlap ratio is not reduced by the disease. However, it is of note that while the overlap ratios (Dice coefficient) of the conditions comprising a motor response were often above 0.60 for the liberal thresholds, and hence can be considered as representing good agreement (Landis & Koch, 1977), the overlap ratios found for the conditions with no motor response were between 0.40 and 0.60 which represents a moderate between-session agreement. For the two more conservative thresholds, most overlap ratios were either between 0.40 and 0.60 (moderate agreement) or below 0.40 (fair to low agreement). Overall our results indicate that to have a reliable index of disease progression or to evaluate the neural effect of treatments, researchers should rely more on statistical comparisons of the condition contrasts across sessions and on comparisons of the average beta values of selected ROIs, rather than on voxel activation comparisons as the latter provide fair to moderate reliability when the task does not include a motor response.

In addition to the two aforementioned thresholds, two other more conservative threshold values were used to calculate the overlap ratio in order to assess the impact of thresholding on this reproducibility measure because, as mentioned above, the overlap ratio is limited by the fact that thresholding an image can exaggerate very small differences and hence lead to considerable differences in the size of the overlap ratio obtained. In the current study the two liberal thresholds ($p<0.001$ and $p<0.005$) led to similar relatively high overlap ratios in the two groups, while the use of two more

conservative threshold values ($p<0.0001$ and $p<0.00001$) led to lower overlap ratios in both groups. This could be due to the fact that some voxels showed few signal differences between the two sessions but with one being just below the threshold and the other being just above the threshold. Alternatively, the current neuroimaging technology, preprocessing treatment (such as smoothing and realignment), and statistical analyses may not be advanced enough and/or optimal to measure session-to-session signal changes on a single voxel basis. Be this as it may, it indicates that threshold values are likely to have an impact on reliability and that more conservative thresholds tend to be associated with lower reliability than less conservative ones. This has obvious implication when using fMRI to assess change in older populations.

We also found some interesting task-related effect on overlap ratios. Notably, memory tasks and phonological tasks yielded comparable overall ratios. The relevant condition appeared to be the presence of a motor response in the task. In both memory and phonological tasks, the inclusion of a motor response resulted in a much higher overlap ratio than when no motor response was included in the task. This is coherent with the literature indicating that sensorimotor tasks produce more reliable brain activation across sessions.

Finally, we assessed fMRI reproducibility with ICC measures in these same ROIs. It is noteworthy that the ICC was calculated here on an individual basis rather than on a group basis (i.e. individual/single measure ICCs rather than average measure ICCs). Results indicated that overall both MCI and healthy controls showed significant ICC on a large number of regions and that the mean ICC values of MCI and healthy older adults

were very close and not statistically different. While significant, ICC values were however of a relatively low magnitude (mean ICC of 0.31 and of 0.36 for healthy controls and MCI, respectively) in comparison to those that have been reported in young healthy individuals (Aron et al., 2006; Specht et al., 2003; Wei et al., 2004). The fact that the ICCs were calculated on the average beta values of the ROI, instead of on the beta value of specific voxels, may however have increased the session-to-session variability. Another finding was that, as observed in studies with young healthy participants, the ICCs values were found to vary greatly as a function of the region analyzed. However, the regional effect on ICCs appears to differ from one group to another, with some regions showing significant ICCs in the MCI group but not in the healthy control group and others showing significant ICC in the healthy control group but not in the MCI group. For healthy controls, ICCs were much lower in Broca's area, hippocampus, and right dorsolateral prefrontal cortex than in the precuneus, left dorsolateral and ventrolateral prefrontal cortex, right ventrolateral prefrontal cortex, and posterior cingulate cortex. For MCI persons, the opposite pattern was found. Yet, those findings suggest that although the fMRI signal is reliable at the group level for both healthy older adults and MCI individuals, it is much less so when examining data on an individual basis. Again, this may arise from the fact that the current neuroimaging technology, preprocessing treatment, and statistical analyses may not be advanced enough and/or optimal enough to reduce within-subject variability and thus to measure session-to-session signal change in a single individual. It could also be due to the sensitivity of the signal to personal factors that vary in time such as fatigue, stress, or other biologically determined factors. It is however noteworthy that most participants were scanned at the same time of the day for the two sessions.

We are aware of the limitations of this study. First, our sample was relatively small and we may have lacked statistical power for some of the analyses even though, although our N was quite consistent with most fMRI studies in clinical populations. Alternatively, it could be argued that a $p<0.001$ threshold is too conservative and may have overshadowed some session-to-session differences. While there is no gold standard for the choice of statistical threshold in fMRI analyses, we believe that the fact that we used multiple reproducibility measures overcomes this limitation. Note also that reliability appears to decrease, not increase, with more conservative threshold. Another limitation could be the use of proportional scaling, a procedure that is used to remove both intersession and intrasession variance in the global signal but that can decrease sensitivity values, and hence may decrease the activation levels, when the global signal is correlated to the experimental paradigm (Gavrilescu et al., 2002; Junghofer, Schupp, Stark, & Vaitl, 2005). The finding of this study should therefore be replicated with other global normalization methods such as grand mean scaling, masking methods or orthogonalization methods. Lastly, the lack of significant task performance differences between the two sessions was judged as a strength because differences in performances might then have an impact on brain activation and may have subsequently limited the interpretation of activation differences. However, it could be also seen as a limitation as the evolution of a disease and/or a pharmalogical or non-pharmalogical intervention are likely to produce a decrease or an increase of the behavioral performance of the participants on the fMRI task. Therefore, these findings will need to be replicated with fMRI tasks that elicit either group differences, or session-to-session differences, in performances.

The findings from this study indicate that MCI individuals exhibit fMRI test-retest reproducibility that are quite comparable to those of healthy older adults, suggesting that the fMRI reproducibility is not modified in an important way by mild cognitive impairments. The results also show that the fMRI signal does not vary significantly at a group level when comparing brain activity in two sessions that are separated by a six-week period, suggesting that this technique could be used as a neural surrogate of pharmalogical or non-pharmalogical approaches to mild cognitive impairment or early Alzheimer's disease (for examples see Goekoop, et al. 2004; Goekoop, et al. 2006; Gron, et al. 2006; Saykin, et al. 2004) as long as the outcome is measured in terms of fMRI signal rather than solely in terms of activation of voxels and as long as it is evaluated at the group level. Indeed, test-retest failed to produce a reliable pattern of significantly activated voxels as there seems to be within-subject variability in the fMRI signal from session to session. This lack of reproducibility at an individual level suggests that precautions should be taken when using fMRI as a diagnostic tool or as a tool to monitor the evolution of the disease. One should first be aware of thresholding effects and rely on multiple thresholds. One should also be aware that task characteristics will affect reliability and that tasks with motor responses should yield higher reproducibility than tasks without motor responses. Lastly, the use of more optimized realignment tools and of higher sizes of full width at half maximum (FWHM) during smoothing may increase reliability by decreasing test-retest differences in voxel localization. Importantly though, the present findings indicate that obtaining reliable test-retest findings with fMRI is not more difficult in a population of older adults with cognitive impairments than in a population of healthy older adults.

References

Aron AR, Gluck MA, Poldrack RA. 2006. Long-term test-retest reliability of functional MRI in a classification learning task. Neuroimage 29(3):1000-6.

Ball K, Berch DB, Helmers KF, Jobe JB, Leveck MD, Marsiske M, Morris JN, Rebok GW, Smith DM, Tennstedt SL and others. 2002. Effects of cognitive training interventions with older adults: a randomized controlled trial. Jama 288(18):2271-81.

Belleville S, Gilbert B, Fontaine F, Gagnon L, Menard E, Gauthier S. 2006. Improvement of episodic memory in persons with mild cognitive impairment and healthy older adults: evidence from a cognitive intervention program. Dement Geriatr Cogn Disord 22(5-6):486-99.

Benton AL, Hamsher K, Varney NR, Spreen O. 1983. Contributions to neuropsychological assessment. New York: Oxford University Press.

Brett M, Anton J-L, Valabregue R, Poline J-P. Region of interest analysis using an SPM toolbox 2002; Sendai, Japan. Available on CD-ROM in NeuroImage, Vol 16, No 2.

Buschke H. 1984. Cued recall in amnesia. Journal of Clinical Neuropsychology 6:433-440.

Cabeza, R., & Nyberg, L. (2000). Imaging cognition II: An empirical review of 275 PET and fMRI studies. *J Cogn Neurosci, 12*(1), 1-47.

Chen EE, Small SL. 2007. Test-retest reliability in fMRI of language: group and task effects. Brain Lang 102(2):176-85.

Craik FI, Winocur G, Palmer H, Binns MA, Edwards M, Bridges K, Glazer P, Chavannes R, Stuss DT. 2007. Cognitive rehabilitation in the elderly: effects on memory. J Int Neuropsychol Soc 13(1):132-42.

Dice, L. (1945). Measures of the amount of ecologic association between species. *Ecology, 26*, 297-302.

Fernandez G, Specht K, Weis S, Tendolkar I, Reuber M, Fell J, Klaver P, Ruhlmann J, Reul J, Elger CE. 2003. Intrasubject reproducibility of presurgical language lateralization and mapping using fMRI. Neurology 60(6):969-75.

Folstein MF, Folstein SE, McHugh PR. 1975. Mini-Mental State: A practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research 12(3):189-198.

Goekoop R, Rombouts SA, Jonker C, Hibbel A, Knol DL, Truyen L, Barkhof F, Scheltens P. 2004. Challenging the cholinergic system in mild cognitive impairment: a pharmacological fMRI study. Neuroimage 23(4):1450-9.

Goekoop R, Scheltens P, Barkhof F, Rombouts SA. 2006. Cholinergic challenge in Alzheimer patients and mild cognitive impairment differentially affects hippocampal activation--a pharmacological fMRI study. Brain 129(Pt 1):141-57.

Gavrilescu, M., Shaw, M. E., Stuart, G. W., Eckersley, P., Svalbe, I. D., & Egan, G. F. (2002). Simulation of the effects of global normalization procedures in functional MRI. *Neuroimage, 17*(2), 532-542.

Gron G, Brandenburg I, Wunderlich AP, Riepe MW. 2006. Inhibition of hippocampal function in mild cognitive impairment: targeting the cholinergic hypothesis. Neurobiol Aging 27(1):78-87.

Hachinski VC, Iliff LD, Zilka E, et al. 1975. Cerebral blood flow in dementia. Archives of Neurology 32:317-320.

Havel P, Braun B, Rau S, Tonn JC, Fesl G, Bruckmann H, Ilmberger J. 2006. Reproducibility of activation in four motor paradigms. An fMRI study. J Neurol 253(4):471-6.

Junghofer, M., Schupp, H. T., Stark, R., & Vaitl, D. (2005). Neuroimaging of emotion: empirical effects of proportional global signal scaling in fMRI data analysis. *Neuroimage, 25*(2), 520-526.

Kaplan EF, Goodglass H, Weintraub S. 1983. The Boston Naming Test (2nd edition). Philadelphia, PA: Lea & Febiger.

Kelly AM, Garavan H. 2005. Human functional neuroimaging of brain changes associated with practice. Cereb Cortex 15(8):1089-102.

Kiehl KA, Liddle PF. 2003. Reproducibility of the hemodynamic response to auditory oddball stimuli: a six-week test-retest study. Hum Brain Mapp 18(1):42-52.

Kong J, Gollub RL, Webb JM, Kong JT, Vangel MG, Kwong K. 2007. Test-retest study of fMRI signal change evoked by electroacupuncture stimulation. Neuroimage 34(3):1171-81.

Kurland J, Naeser MA, Baker EH, Doron K, Martin PI, Seekins HE, Bogdan A, Renshaw P, Yurgelun-Todd D. 2004. Test-retest reliability of fMRI during nonverbal semantic decisions in moderate-severe nonfluent aphasia patients. Behav Neurol 15(3-4):87-97.

Landis, J. R., & Koch, G. G. (1977). The measurement of observer agreement for categorical data. *Biometrics, 33*, 159-174.

Liu JZ, Zhang L, Brown RW, Yue GH. 2004. Reproducibility of fMRI at 1.5 T in a strictly controlled motor task. Magn Reson Med 52(4):751-60.

Loubinoux I, Carel C, Alary F, Boulanouar K, Viallard G, Manelfe C, Rascol O, Celsis P, Chollet F. 2001. Within-session and between-session reproducibility of cerebral sensorimotor activation: a test--retest effect evidenced with functional magnetic resonance imaging. J Cereb Blood Flow Metab 21(5):592-607.

Machielsen WC, Rombouts SA, Barkhof F, Scheltens P, Witter MP. 2000. FMRI of visual encoding: reproducibility of activation. Hum Brain Mapp 9(3):156-64.

Maldjian JA, Laurienti PJ, Driskill L, Burdette JH. 2002. Multiple reproducibility indices for evaluation of cognitive functional MR imaging paradigms. AJNR Am J Neuroradiol 23(6):1030-7.

Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH. 2003. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. Neuroimage 19(3):1233-9.

Manoach DS, Halpern EF, Kramer TS, Chang Y, Goff DC, Rauch SL, Kennedy DN, Gollub RL. 2001. Test-retest reliability of a functional MRI working memory paradigm in normal and schizophrenic subjects. Am J Psychiatry 158(6):955-8.

Marshall I, Simonotto E, Deary IJ, Maclullich A, Ebmeier KP, Rose EJ, Wardlaw JM, Goddard N, Chappell FM. 2004. Repeatability of motor and working-memory tasks in healthy older volunteers: assessment at functional MR imaging. Radiology 233(3):868-77.

Mattis S. 1976. Mental status examination for organic mental syndrome in the elderly patient. In: Bellak L, Karasu TB, editors. Geriatric Psychiatry. New York: Grune & Stratton.

Miki A, Raz J, van Erp TG, Liu CS, Haselgrove JC, Liu GT. 2000. Reproducibility of visual activation in functional MR imaging and effects of postprocessing. AJNR Am J Neuroradiol 21(5):910-5.

Miller MB, Van Horn JD, Wolford GL, Handy TC, Valsangkar-Smyth M, Inati S, Grafton S, Gazzaniga MS. 2002. Extensive individual differences in brain activations associated with episodic retrieval are reliable over time. J Cogn Neurosci 14(8):1200-14.

Neumann J, Lohmann G, Zysset S, von Cramon DY. 2003. Within-subject variability of BOLD response dynamics. Neuroimage 19(3):784-96.

Petersen RC, Morris JC. 2005. Mild cognitive impairment as a clinical entity and treatment target. Arch Neurol 62(7):1160-3; discussion 1167.

Raemaekers M, Vink M, Zandbelt B, van Wezel RJ, Kahn RS, Ramsey NF. 2007. Test-retest reliability of fMRI activation during prosaccades and antisaccades. Neuroimage 36(3):532-42.

Rapp S, Brenes G, Marsh AP. 2002. Memory enhancement training for older adults with mild cognitive impairment: a preliminary study. Aging Ment Health 6(1):5-11.

Regard M. 1981. Cognitive rigidity and flexibility: a neuropsychological study. University of Victoria, Canada.

Rey A. 1959. Test de copie d'une figure complexe: manuel. Paris: Les éditions du centre de psychologie appliquée.

Rombouts SA, Barkhof F, Hoogenraad FG, Sprenger M, Scheltens P. 1998. Within-subject reproducibility of visual activation patterns with functional magnetic resonance imaging using multislice echo planar imaging. Magn Reson Imaging 16(2):105-13.

Rombouts SA, Barkhof F, Hoogenraad FG, Sprenger M, Valk J, Scheltens P. 1997. Test-retest analysis with functional MR of the activated area in the human visual cortex. AJNR Am J Neuroradiol 18(7):1317-22.

Rutten GJ, Ramsey NF, van Rijen PC, van Veelen CW. 2002. Reproducibility of fMRI-determined language lateralization in individual subjects. Brain Lang 80(3):421-37.

Saykin AJ, Wishart HA, Rabin LA, Flashman LA, McHugh TL, Mamourian AC, Santulli RB. 2004. Cholinergic enhancement of frontal lobe activity in mild cognitive impairment. Brain 127(Pt 7):1574-83.

Shattuck, D. W., Sandor-Leahy, S. R., Schaper, K. A., Rottenberg, D. A., & Leahy, R. M. (2001). Magnetic resonance image tissue classification using a partial volume model. *Neuroimage, 13*(5), 856-876.

Signoret JL. 1991. Batterie d'efficience mnésique BEM 144. Paris: Elsevier.

Specht K, Willmes K, Shah NJ, Jancke L. 2003. Assessment of reliability in functional imaging studies. J Magn Reson Imaging 17(4):463-71.

Stark R, Schienle A, Walter B, Kirsch P, Blecker C, Ott U, Schafer A, Sammer G, Zimmermann M, Vaitl D. 2004. Hemodynamic effects of negative emotional pictures - a test-retest analysis. Neuropsychobiology 50(1):108-18.

Swallow KM, Braver TS, Snyder AZ, Speer NK, Zacks JM. 2003. Reliability of functional localization using fMRI. Neuroimage 20(3):1561-77.

Van der Linden M, Adam S, Agniel A, Baisset-Mouly C, Bardet F, Coyette F, Desgranges B, Deweer B, Ergis AM, Gély-Nargeot MC and others. 2004. L'évaluation de troubles de la mémoire: présentation de quatre tests de mémoire épisodique (avec étalonnage). Marseille: Solal.

Wagner K, Frings L, Quiske A, Unterrainer J, Schwarzwald R, Spreer J, Halsband U, Schulze-Bonhage A. 2005. The reliability of fMRI activations in the medial temporal lobes in a verbal episodic memory task. Neuroimage 28(1):122-31.

Waldvogel D, van Gelderen P, Immisch I, Pfeiffer C, Hallett M. 2000. The variability of serial fMRI data: correlation between a visual and a motor task. Neuroreport 11(17):3843-7.

Wechsler D. 1997. *Wechsler Adult Intelligence Scale-III* New York: Psychological Corporation.

Wei X, Yoo SS, Dickey CC, Zou KH, Guttmann CR, Panych LP. 2004. Functional MRI of auditory verbal working memory: long-term reproducibility analysis. Neuroimage 21(3):1000-8.

Yesavage JA. 1988. Geriatric Depression Scale. Psychopharmacological Bulletin 24:709-711.

Yetkin FZ, McAuliffe TL, Cox R, Haughton VM. 1996. Test-retest precision of functional MR in sensory and motor task activation. AJNR Am J Neuroradiol 17(1):95-8.

Acknowledgement

This work was supported in part by a grant from the FRSQ Repar and Repric and by a grant from CIHR to SB. SB receives an FRSQ chercheur-national. FC was supported by a scholarship from CIHR. We thank Samira Mellah for assistance in task construction and data collection, Étienne Vachon-Presseau for his suggestions and comments and Luke Henry for editorial assistance. The authors have reported no conflicts of interest.

Table I

Scores on the neuropsychological tasks for the two groups. SD is in parenthesis.

	Controls n = 10	MCI n = 10
MDRS (/144)	140.40 (3.10)	133.30 (8.51) *
MMSE (/30)	29.10 (0.74)	27.60 (1.65) *
MOCA (/30)	26.75 (1.75)	
GDS (/15)	1.38 (2.45)	3.29 (2.98)
Hachinski (/18)		2.20 (2.57)
Boston Naming Test (/15)		12.40 (2.68)
BEM Immediate recall (/12)		6.62 (1.19)
BEM Delayed recall (/12)		5.69 (1.36)
RL/RI-16 3rd free recall (/16)	12.20 (1.87)	7.80 (4.78) *
RL/RI-16 delayed free recall (/16)	13.50 (1.18)	8.50 (4.48) **
Copy of Rey's Figure: time		241.30(123.54)
Copy of Rey's Figure: score (/36)		28.30 (4.18)
Stroop 3rd plate time		37.11 (19.02)
Stroop 3rd plate errors		2.60 (3.06)
Benton Judgment of line orientation (/30)		20.70 (4.67)
Coding (WAIS-III, scaled score)		9.30 (2.21)

Note. impairment relative to the controls at * $p < 0.05$; ** at $p < 0.01$

Table II

Activated clusters (>10 voxels) for the comparison of sessions 1 and 2 of memory encoding with cluster size, peak voxel MNI coordinates and corresponding t-values.

Activates areas (Brodmann area) ($p < 0.001$)	Cluster Size	x	y	z	t value
Healthy Controls: Encoding Session 1 > Session 2					
Right putamen	18	18	0	6	4.06
Left putamen	25	-24	0	21	4.04
Left inferior/middle temporal gyrus (21)	12	-57	-9	-18	3.90
MCI: Encoding Session 1 > Session 2					
Left middle frontal gyrus (11)	15	-36	51	-9	4.27

Table III

Activated clusters (>10 voxels) for the comparison of sessions 1 and 2 of phonological processing without motor responses with cluster size, peak voxel MNI coordinates and corresponding t-values.

Activates areas (Brodmann area) ($p < 0.001$)	Cluster Size	x	y	z	t value
Healthy Controls: Phonological processing without motor responses Session1>Session2					
Left putamen	19	-24	0	21	3.67

Table IV

Activated clusters (>10 voxels) for the comparison of sessions 1 and 2 phonological processing with motor responses with cluster size, peak voxel MNI coordinates and corresponding t-values.

Activates areas (Brodmann area) ($p < 0.001$)	Cluster Size	x	y	z	t value
MCI: Phonological processing with motor responses Session 1 > Session 2					
Left cerebellum	26	-21	-69	-39	4.08

Table V.

Single measures intraclass correlation of ROIs for both groups & for the four conditions

	Controls				MCI			
Condition	1	2	3	4	1	2	3	4
Broca's area (BA 44)	0.30	0.38	-0.18	0.39	0.31	0.60*	0.13	-0.13
Precuneus bilaterally (BA 7)	-0.1	0.56*	-0.21	0.62*	0.48*	0.63*	0.64*	0.79***
Hippocampus bilaterally	0.02	-0.05	-0.25	0.29	-0.08	0.48*	0.19	0.50*
Left dorsolateral PFC (BA 9, 46)	0.50*	0.57*	0.38	0.59*	0.13	0.29	0.11	0.40
Right dorsolateral PFC (BA 9, 46)	0.22	0.24	0.09	0.36	0.36	0.61*	0.60*	0.70**
Left ventrolateral PFC (BA 45, 47)	0.16	0.59*	0.05	0.42	-0.17	0.40	-0.23	0.32
Right ventrolateral PFC (BA 45, 47)	0.36	0.79***	0.24	0.90***	0.43	0.33	0.27	0.17
Posterior cingulate cortex	0.10	0.76**	0.05	0.72**	0.22	0.61*	0.60*	0.74**

Note. F-test (with a reference test-value of 0) significant at * $p < 0.05$; ** at $p < 0.01$; *** at $p < 0.001$

Figure 1. Activations for the encoding condition a) for session one in healthy controls group b) in session two in healthy controls group c) for session one in MCI group d) for session two in MCI group.

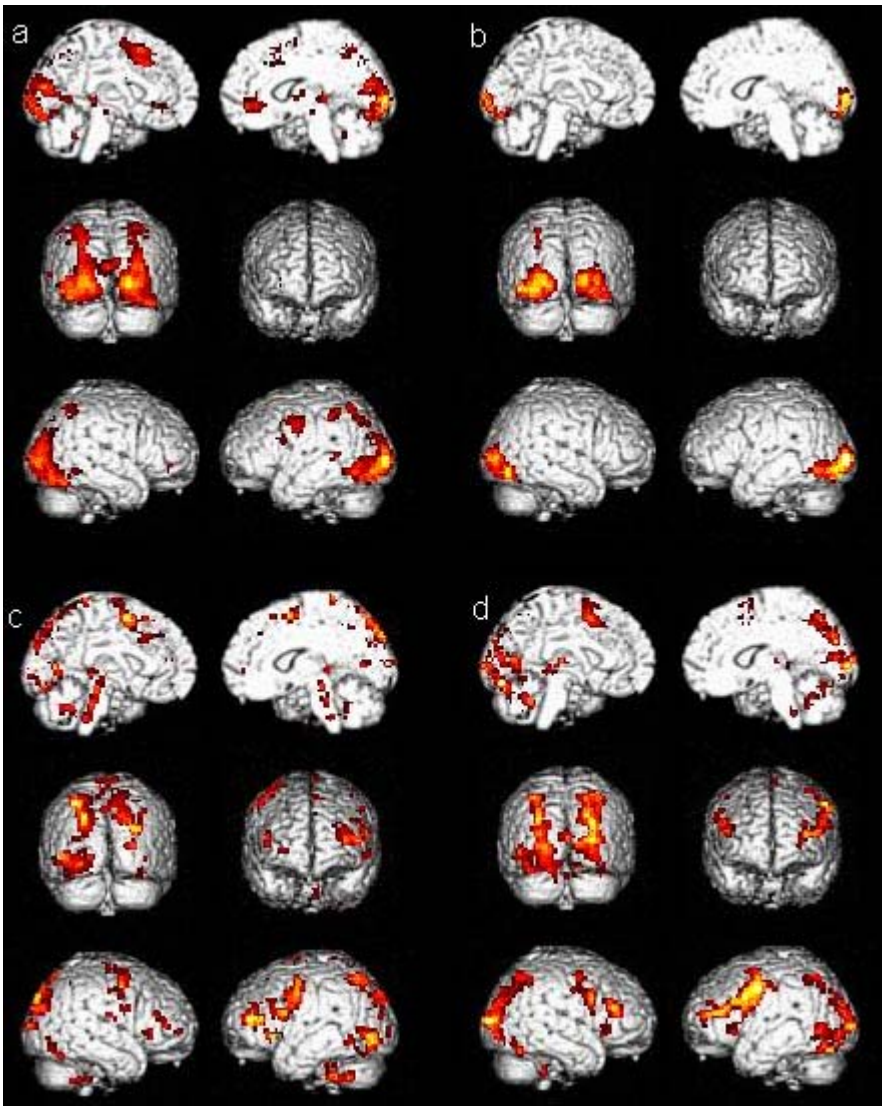


Figure 2. Activations for the retrieval condition a) for session one in healthy controls group b) in session two in healthy controls group c) for session one in MCI group d) for session two in MCI group.

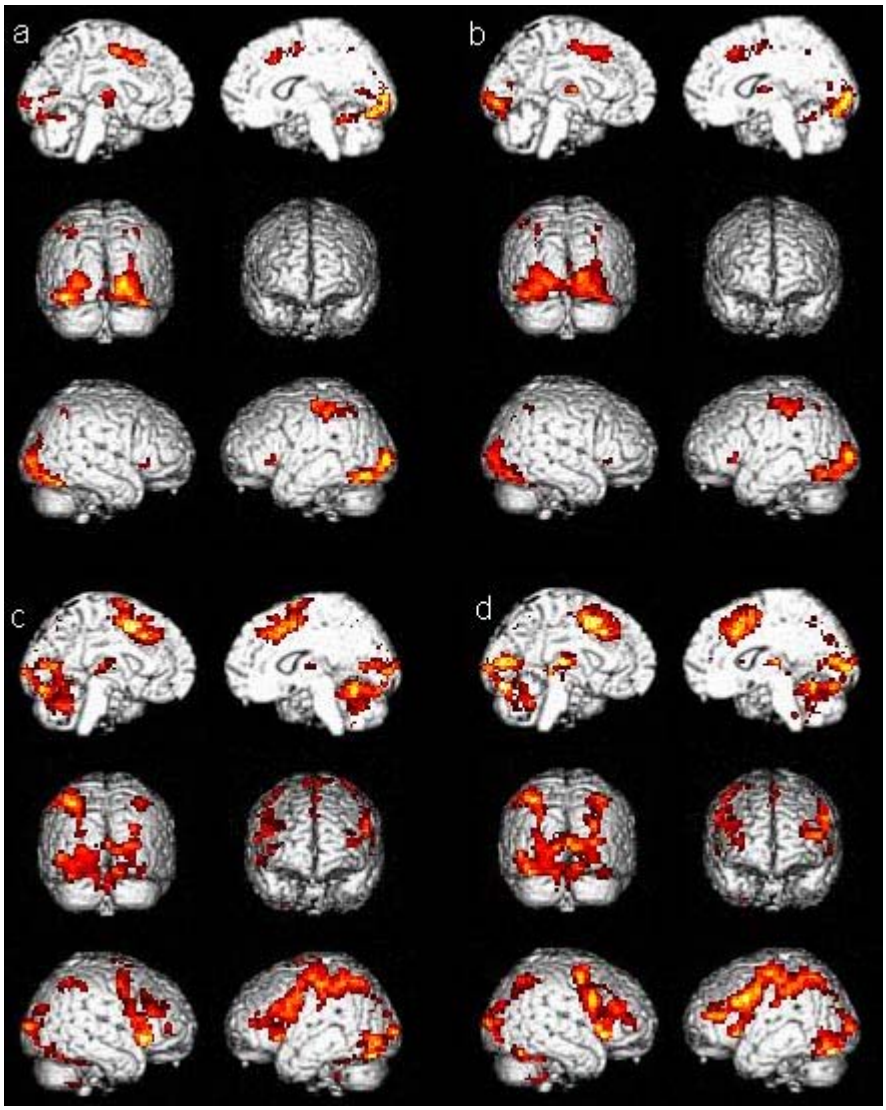


Figure 3. Activations for the phonological processing without a motor response condition a) for session one in healthy controls group b) in session two in healthy controls group c) for session one in MCI group d) for session two in MCI group.

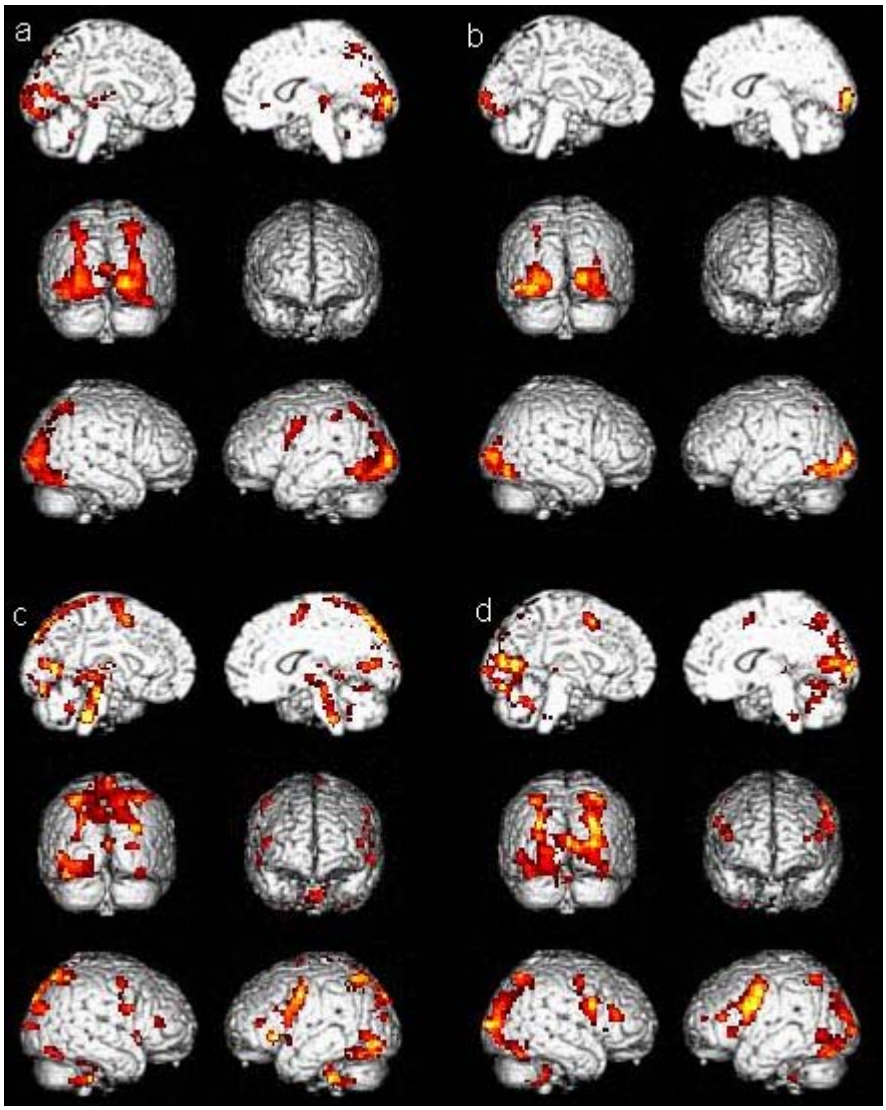


Figure 4. Activations for the phonological processing with a motor response condition a) for session one in healthy controls group b) in session two in healthy controls group c) for session one in MCI group d) for session two in MCI group.

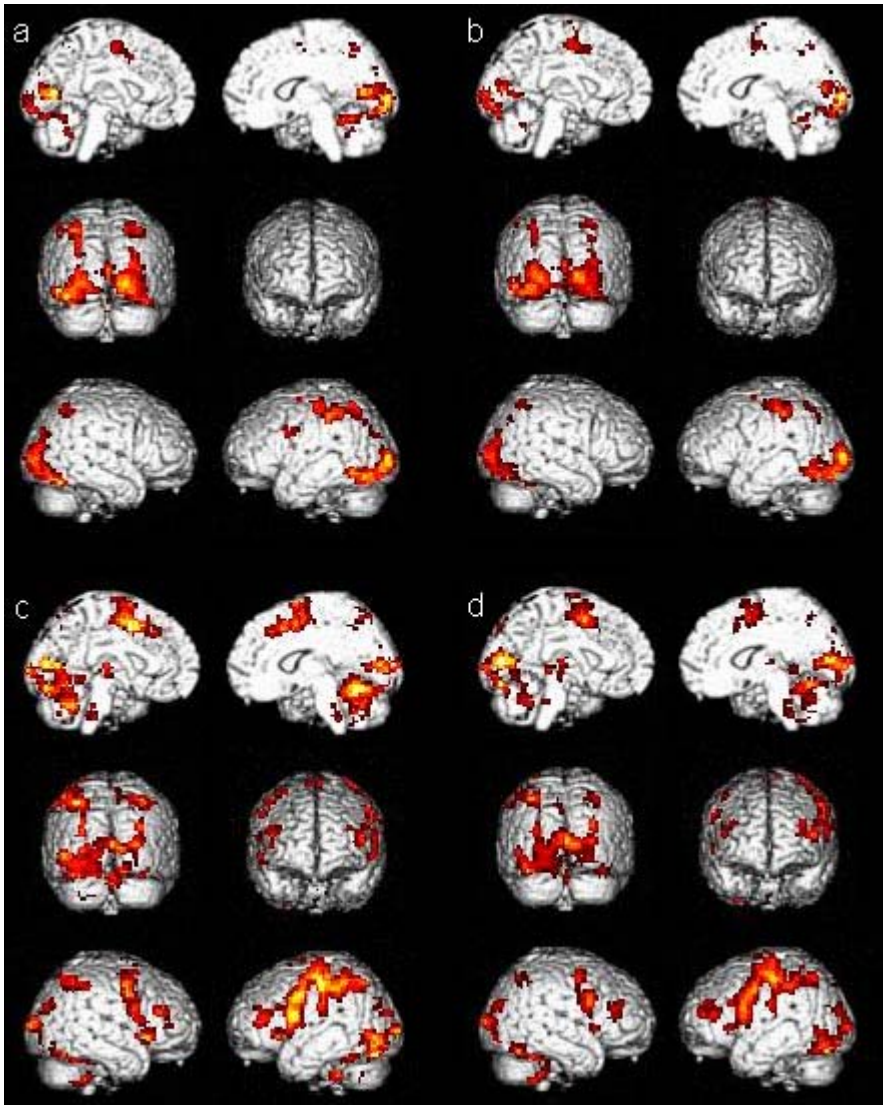
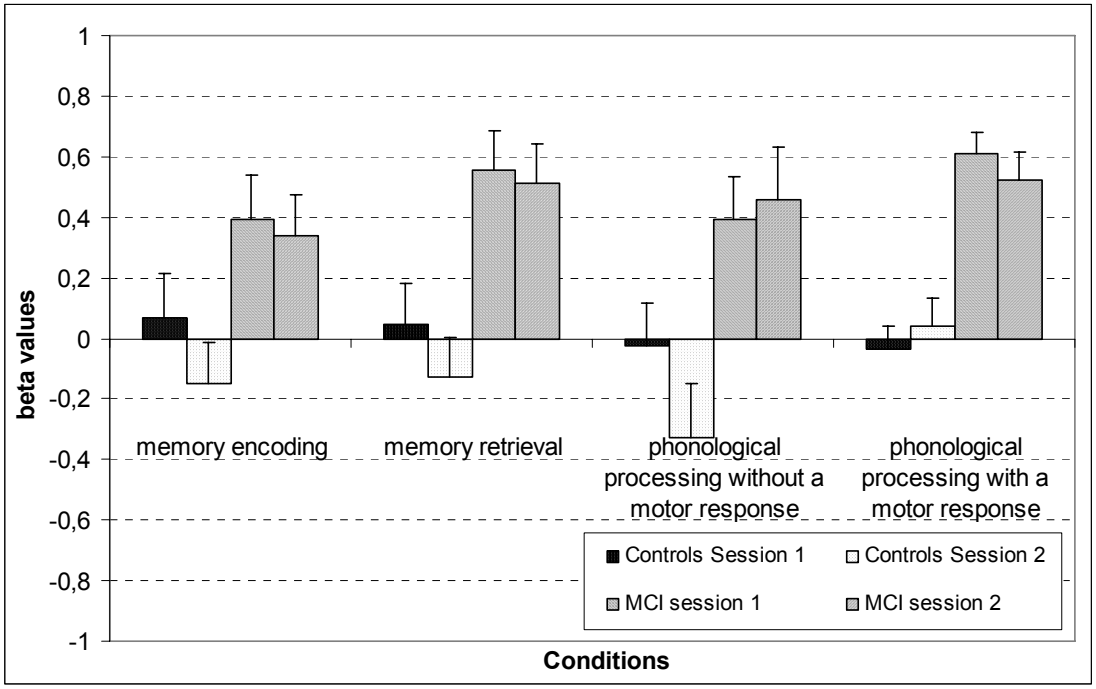


Figure 5. Beta values in Broca's area (BA 44) for the two groups during the four conditions and during the two sessions.



CHAPITRE 3

Article n° 2

Functional neuroanatomy of the encoding and retrieval processes of verbal episodic memory in MCI

Francis Clément, Sylvie Belleville & Samira Mellah

Cortex 2010; 46(8): 1005-1015.

Abstract

Introduction: The goal of this study was to explore the association between disease severity and performance on brain activation associated with episodic memory encoding and retrieval in persons with mild cognitive impairment. **Method:** This was achieved by scanning 12 MCI persons and 10 age- and education-matched healthy controls while encoding words and while retrieving them in a recognition test. **Results:** Behaviorally, there was no significant group difference on recognition performance. However, MCI and healthy controls showed different patterns of cerebral activation during encoding. While most of these differences demonstrated reduced activation in the MCI group, there were areas of increased activation in the left ventrolateral prefrontal cortex. Reduced activation was found in brain areas known to be either structurally compromised or hypometabolic in AD. In contrast, very few group differences were associated with retrieval. Correlation analyses indicated that increased disease severity, as measured with the Mattis Dementia Rating Scale, was associated with smaller activation of the right middle and superior temporal gyri. In contrast, recognition success in MCI persons was associated with larger activation of the left ventrolateral prefrontal cortex during the encoding phase. **Conclusion:** Overall, our results indicate that most of the memory-related cerebral network changes in MCI persons occur during the encoding phase. They also suggest that a prefrontal compensatory mechanism could occur in parallel with the disease-associated reduction of cerebral activation in temporal areas.

Key words: neuroimaging, dementia, ageing, memory, cognition

1. Introduction

People with mild cognitive impairment (MCI) experience more marked memory deficits than what would be expected based on their age and education, yet fail to reach criteria for dementia (Petersen et al., 2001; Gauthier et al., 2006). They are, however, at risk of developing AD and voxel-based morphometry and MRI volumetry studies of MCI show that this condition is associated with marked reduction in hippocampal and entorhinal cortex volumes (Whitwell et al., 2007; Xu et al., 2000; Pennanen et al., 2005; Pennanen et al., 2004). Moreover, the atypical atrophy in MCI persons is positively correlated with conversion to AD (Erten-Lyons et al., 2006; Korf et al., 2004; Jack et al., 1999). The aforementioned regions are typically involved in episodic memory and a certain number of studies have investigated whether those structural changes in MCI are associated with effects on brain activation while completing episodic memory tasks. Understanding how MCI modifies the brain's physiological response to cognitive events is critical because such functional changes may represent early indicators of neurodegenerative diseases. In addition, activation studies may provide crucial information about how brain networks support memory performance in persons with MCI and whether these brain networks differ qualitatively or quantitatively from those supporting memory in healthy older adults.

A number of studies have documented the alterations of the medial temporal lobe in MCI individuals and in early AD (Mitchell et al., 2002; Markesbery et al., 2006). In

addition, there is also some recent evidence that the basal forebrain cholinergic system, which provide cholinergic innervations to all cortical areas, appears to show some of the earliest AD neuropathology (Auld et al., 2002; Mesulam et al., 2004). This may explain the fact that functional brain imaging studies have observed brain dysfunctions that extend beyond the medial temporal lobe area and alter the functioning of large neural networks involved in memory (e.g.: Johnson et al., 2006; Petrella et al., 2007; Ries et al., 2005; Kircher et al., 2007; Heun et al., 2007). However, whether those alterations result in hyper or hypoactivation is unclear as well as the more specific localization of those impaired networks, particularly along the anterior/posterior axis. While a number of studies of memory encoding have found decreased activation in the medial temporal lobe (Johnson et al., 2006; Machulda et al., 2003; Trivedi et al., 2006) and in the prefrontal cortex of persons with MCI (Dannhauser et al., 2008; Mandzia et al., 2002; Mandzia et al., 2007), some studies have reported that MCI persons or persons at risk for AD have more activation than healthy older adults in the medial temporal lobe (Bookheimer et al., 2000; Kircher et al., 2007; Dickerson et al., 2005; Hamalainen et al., 2007), in the prefrontal cortex (Bookheimer et al., 2000; Bondi et al., 2005; Han et al., 2006), and in posteromedial cortices (Petrella et al., 2007). Studies of the retrieval phase of episodic memory have also reported conflicting results, with some of them reporting decreased activations in the prefrontal cortex (Mandzia et al., 2002; Mandzia et al., 2007) and in posteromedial cortices (Ries et al., 2005), while another study reports increased activations of the prefrontal cortex (Heun et al., 2007).

Our literature review suggests that across studies, persons with MCI and healthy controls show more areas of reliable brain activation differences during the encoding

phase when compared with the retrieval phase. This may suggest that encoding is particularly vulnerable to the early stage of AD. However, in most studies, participants were scanned either while learning the list (for encoding studies) or while recognizing items (for retrieval studies) and differences in patient sample and design complicates direct comparison of their results. Investigating both the encoding and retrieval phases in the same set of participants facilitates comparison of the activation associated with the two phases and can thus provide data regarding their differential sensitivity to the disease. It can also help us to understand whether both phases would be associated with similar localisation and pattern of brain changes.

The inconsistent findings in the literature can also arise from the fact that MCI criteria are extremely variable and different studies include MCI participants that may diverge in terms of their clinical characteristics. Group differences in levels of severity is an important issue to this regard. Studies that have assessed the natural history of cognitive deficits in MCI have reported that those persons experience a gradual increase in their symptom severity, due to accumulation of AD pathology (Bennett et al., 2002). Differences in severity may reveal themselves to be a determining factor in accounting for differences in the patterns of brain activation in neurodegenerative diseases (Prvulovic et al., 2005; Celone et al., 2006). Within this perspective, a recent model has proposed that milder brain neuropathologies in early AD might lead to a mild decrease in processing efficiency accompanied by a compensatory increase in neuron recruitment. As the disease progresses and neuropathologies accumulate, processing capacity would further decrease and would pose limits on the capacity for compensatory neuronal recruitment (Prvulovic et al., 2005). Based on this model, it is expected that MCI

persons situated on the mild end of the disease severity continuum would tend to show more brain activation than healthy controls, whereas MCI persons with more severe deficits and closer to AD would tend to show less brain activation than healthy controls. One study has reported results that are congruent with this hypothesis. Using a face-name associative encoding task, Celone et al. (2006) reported hippocampal hyperactivation in MCIs with less severe cognitive impairments relative to healthy controls, and hippocampal hypoactivation in MCIs with more severe cognitive impairments. It must be noted however that the MCI persons in this study were chosen based on different criteria than the ones used in the other studies. Generalizing these findings to individuals meeting current MCI criteria would have important implications for the assessment and follow-up of these individuals, for the understanding and integration of the results found in the literature, and for the comprehension of the brain response to neurodegenerative injuries.

The goal of this study was to assess the role of disease severity on the brain activation of persons with MCI during both the encoding and retrieval phases of a verbal episodic memory task. Furthermore, we wanted to explore the impact of performance on the nature and extent of brain activation. This was assessed in the prefrontal cortex and in the temporal lobe, two key regions for memory processes. In line with the literature, we hypothesized that more group differences in brain activation would be observed during the encoding phase than during the retrieval phase. We also hypothesized that performances would be correlated with brain activation in the prefrontal cortex for the healthy controls group, as this region has been linked to retrieval success in both healthy younger (Wagner et al., 1998) and healthy older adults. It is unclear whether a similar association is present or not in MCI as Dannhauser and collaborators (2008) have failed

to find a correlation between prefrontal activation and performance in persons with MCI during a verbal memory encoding task that promoted interference effects. Presence of a larger activation of the prefrontal areas in MCI associated with a positive correlation between prefrontal activation and memory performance would be consistent with compensatory mechanisms whereas a lack of correlation would not.

Methods

Participants

Twelve persons with MCI (9 females and 3 males) and 10 healthy older adults (8 females and 2 males) took part in this study. Persons with MCI had a mean age of 67.83 years (SD = 7.49) and had a mean of 13.25 (SD = 3.96) years of education. Healthy older adults had a mean age of 71.70 years (SD = 7.62), with an average of 12.50 (SD = 2.68) years of education. French was the first language of all participants.

Participants with MCI were recruited from memory clinics and met the criteria proposed by Petersen (Petersen et al., 1999; Petersen et al., 2001; Winblad et al., 2004) for single (n=3) or multiple domain (n=9) amnestic MCI: they had a subjective memory complaint and performed at least 1.5 SD below the average level of persons of similar age and education on standardized memory tests, they showed no global cognitive impairment on the basis of the MMSE, nor any significant impact on daily functions as measured by the SMAF functional impairment scale, a 29-item scale that measures functional ability in five areas of daily living (activities of daily living, mobility, communication, mental functions and instrumental activities of daily living) (Desrosiers et al., 1995), and clinical interview, and failed to meet criteria for dementia. MCI

participants went through an extensive neuropsychological evaluation that covered episodic memory (cued and free word recall task, RL/RI-16; Buschke, 1984; Van der Linden et al., 2004, text memory of the BEM; Signoret, 1991, and recall of Rey's Complex Figure; Rey, 1959), executive functions (third card of Victoria Stroop; Regard, 1981, and copy of Rey's Complex Figure; Rey, 1959), visuospatial processing (Benton Judgment of line orientation; Benton et al., 1983), information processing speed (Coding of the WAIS-III; Wechsler, 1997), language (Boston Naming Test; Kaplan et al., 1983), and global cognitive functions (Mattis Dementia Rating Scale, MDRS; Mattis, 1976, and Mini-Mental State Examination, MMSE; Folstein et al., 1975). The MDRS is a measure of cognitive abilities that includes 36 tasks measuring five cognitive domains (Attention, Initiation, Construction, Reasoning, and Memory), with a maximum total score of 144. This scale bears many advantages over the MMSE: it is not curtailed by ceiling effects and it investigates a broad range of cognitive functions which might make it more sensitive to the mild cognitive deficits characterizing MCI. The MDRS has strong internal consistency (correlation coefficient of .90), and is a useful test for quantifying the degree of impairment in individuals with organic mental syndrome (Gardner et al., 1981). This test is widely used as a measure of global cognitive functions in older patients with cognitive impairment (Clement et al., 2008; Chetelat et al., 2005; Furio et al., 2007; Graff-Radford et al., 2007). MCI persons also received a medical, neurological and neuroradiological examination to exclude the presence of any other systemic, neurological or psychiatric condition that could explain their cognitive difficulties. Healthy older adults were recruited from the community and they were tested with a subset of the neuropsychological tests used with MCI (MDRS, MMSE, RL/RI-16). All healthy controls performed within normal limits (determined on an individual basis, i.e.

above cut-off score) on the MDRS, MMSE, and RL/RI-16, ensuring that they did not suffer from mild cognitive deficits.

Participants all met the following exclusion criteria: diagnosis of probable AD or other form of dementia, history of neurological or severe psychiatric disorder, history of cardiovascular disease, alcoholism, drug addiction, using psychoactive drugs or a general anesthesia during the last six months.

This study was approved by the Institut Universitaire de Gériatrie de Montréal Human Ethics Committee and by the Comité conjoint d'Évaluation Scientifique du Regroupement de Neuroimagerie du Québec (CÉS-RNQ) and was part of an intervention study as a control condition.

Stimuli

Six lists of eight one- to three- syllable words were used for learning in the encoding phase. Items were all concrete words and they were matched across lists in terms of average word frequency, familiarity, semantic category membership, and concreteness values, all obtained from a French words database, Lexique (www.lexique.org) . Six lists of eight words were also used for the retrieval phase. Each list contained four old words that were part of the corresponding encoding list and four new words. The new words were matched to the old words in terms of the number of syllables, frequency of use, semantic category, and concreteness values, based again on a French words database (Lexique).

Procedure

The task was programmed on E-prime and stimuli were visually presented and mirror-projected. Subjects wore goggles appropriate for MRI if their vision needed correction. Two days prior to and just before scanning, participants were trained on the task and were exposed to the sound of the scanner.

The fMRI episodic memory task consisted of two runs: the encoding run was composed of six alternating blocks series of rest (28 sec each) and intentional encoding (40 sec each) and the retrieval run was composed of six alternating blocks series of rest (28 sec each) and retrieval (40 sec each). During rest, subjects were instructed to close their eyes and relax. During encoding, subjects were asked to memorize the words that were shown on the screen (8 words per block, 4 sec presentation rate, 1 sec interstimulus interval). During retrieval, subjects were asked to perform an old-new recognition judgment using a two-button response. Eight words were presented, half of which were presented in the preceding encoding blocks. In addition, a brief instruction (4 sec) was presented to the subjects prior to each encoding and retrieval blocks. The instruction blocks were modeled as a condition of no-interest. The retrieval phase was included in a separate run after participants had encoded all lists. As a result, the encoding and retrieval of a particular list was separated by about 15 minutes during which participants were encoding/retrieving other items. This procedure precluded reliance on working memory rehearsal.

Data acquisition

Magnetic Resonance Imaging (MRI) was performed using a Siemens 3-T whole-body system (Siemens, Erlangen, Germany) at the Institut Universitaire de Gériatrie de

Montréal. A 3-D structural image was taken at the end of the session and consisted of a sagittal T1-weighted 3D-MPRAGE sequence (TR/TE = 1950/3.93 ms, flip angle = 15 deg; 176 slices, voxel size = 1 mm x 1 mm x 1 mm, field of view = 256 mm, matrix = 256*256). Functional MR images were acquired using Gradient-Echo Echo-Planar imaging sequences (GE-EPI) sensitive to blood oxygen level-dependent (BOLD) contrast (TR/TE = 2000/30 ms, flip angle = 90 deg; 31 interleaved slices, voxel size = 3.75 mm x 3.75 mm x 5 mm with a gap of 1 mm, field of view = 240 mm, matrix = 64*64).

Image processing and data analysis

Data were analyzed in MATLAB 7.0 (http://www.mathworks.com) using the statistical parametric mapping software SPM5 (http://www.fil.ion.ucl.ac.uk/spm/). Before statistical analysis, functional images were converted into Analyze format and unwarped. Functional volumes of each subject were then realigned to the first acquired volume in the session and a mean realigned volume was created for each subject. All the realigned volumes of each subject were spatially normalized into the Montreal Neurological Institute (MNI) stereotactic space and spatially smoothed with an 8-mm Gaussian kernel. Low-frequency noise was removed with a high-pass filter of 256 sec. Global changes in fMRI response from scan to scan were removed by proportionally scaling each volume to a common global mean voxel value. A single-subject analysis was carried out in order to evaluate the individual contrasts (encoding vs rest and retrieval vs rest) for each subject. A Random Effects (RFX) Analysis was then performed by calculating, for each group, a two way ANOVA with Groups (healthy older adults, MCI) as a between-subjects factor and Conditions (encoding, retrieval) as a within-subjects factor, with non-sphericity correction, replications over subjects, and with

correlated repeated measures. An uncorrected threshold of $p < .001$ with 10 continguous voxels was used for within-group comparisons and an uncorrected threshold of $p < .005$ with 10 continguous voxels was used for between-group comparisons.

In a second step, the average beta values of each between-group comparison significant cluster in the frontal lobe and in the temporal lobe for both encoding and retrieval were extracted with marsbar (Brett et al., 2002) and correlated in SPSS 13.0 (Statistical Product and Service Solution, http://www.spss.com) to the behavioural performance of the subjects. For MCI participants, these averaged beta values were also correlated to their MDRS scores.

Results

Sociodemographic data

Two independent t-tests were computed on the dependant variables age and education to assess whether the groups were properly matched on the sociodemographic variables age and education. No significant age, $t(20) = 1.19$, N.S., and education effects, $t(20) = -.51$, N.S., were found.

Neuropsychological evaluation

Independent t-tests were also computed on the scores obtained by the two groups on the neuropsychological tests. As illustrated in Table 1 and as expected, MCI participants obtained significantly lower scores than healthy controls on the MDRS, $t(20) = 2.43$, $p < .05$, MMSE, $t(20) = 2.32$, $p < .05$, on the 3rd free recall of the RL/RI-16, $t(20) = 3.16$, $p < .01$, and on the delayed recall of the RL/RI-16, $t(20) = 3.94$, $p < .01$.

Behavioral data

The mean percentage of correctly recognized words was 65.85% (SD = 11.07) for the MCI group[1] and 72.00% (SD = 10.85) for the healthy control group. An independent t-test indicated that the small group difference was not statistically significant, t(18) = 1.25, N.S. To avoid possible response bias, the corrected recognition rate (*P*hit – *P*false alarms) was also calculated. The MCI group showed a mean corrected recognition rate of 42.25% (SD = 21.98) whereas the control group showed a mean corrected recognition rate of 50.47% (SD = 16.66). Again, independent t-test indicated that the group difference was not statistically significant, t(18) = 0.94, N.S.

Neuroimaging data

Within-group comparisons

Controls. During encoding, the group of healthy controls showed activations in the left parahippocampal gyrus, in the right cerebellum and bilaterally in the anterior and posterior cingulate gyrus, in the occipital lobe (Brodmann areas 17,18,19), in the occipitotemporal regions (Brodmann area 37), in the parietal lobe (precuneus, supramarginal and angular gyri), in the medial prefrontal cortex (Brodmann areas 10,11, and 32), in the premotor area, in the thalamus, and in the basal ganglia (Figure 1a). Similar activations were found during retrieval. Activations were found in the left thalamus, the left cerebellum anterior, the left supramarginal gyrus, the left (Brodmann area 47) and right (45) inferior frontal gyrus, the right premotor area, and bilaterally in the posterior cingulate gyrus, the sensorimotor area, the precuneus, the occipital lobe

(Brodmann areas 17,18,19), and the occipitotemporal regions (Brodmann area 37). Note that no activations were found in the medial temporal lobe during retrieval (Figure 1b).

MCI. During encoding, MCI persons also showed activations in the left parahippocampal gyrus, in the left and in the right hippocampi, and bilaterally in the inferior prefrontal gyrus (Brodmann areas 44, 45, and 47), in the orbitofrontal regions (Brodmann area 10), in the dorsolateral prefrontal cortex (Brodmann areas 9 and 46), in the premotor region, in the anterior and posterior cingulate gyrus, in the precuneus, in the occipital lobe (Brodmann areas 17,18,19), in the occipitotemporal regions (Brodmann area 37), in the left thalamus, in the basal ganglia, in the medulla, in the pons, in the midbrain, and in the cerebellum (Figure 1c). During retrieval, MCI participants activated regions similar to the ones observed during encoding. Activations were found in the left insula, and bilaterally in the anterior and posterior cingulate gyrus, the parahippocampal gyrus, the inferior frontal gyrus (Brodmann areas 44, 45 and 47), the dorsolateral prefrontal cortex (Brodmann area 46), the premotor region, the sensorimotor region, the precuneus, the supramarginal gyrus, the occipitotemporal regions (Brodmann area 37), the occipital lobe (Brodmann areas 17,18,19), the thalamus, the basal ganglia, and the cerebellum (Figure 1d). As was the case for healthy controls, MCI persons did not show activation of the medial temporal lobe during retrieval.

Between-group comparisons

A number of significant activation differences were found between the two groups during the encoding phase as shown in Table 2 and described below.

Controls>MCI Encoding. During encoding, MCI persons showed less activation than healthy controls in the right middle and superior temporal gyrus, bilaterally in the occipital lobe, in the right thalamus, and in the right anterior cingulate gyrus and right medial frontal lobe.

Controls<MCI Encoding. MCI participants showed more activation than healthy controls in the left ventrolateral prefrontal cortex during the encoding phase.

Controls>MCI Retrieval. During retrieval, MCI persons showed less activation than healthy controls in the medial frontal lobe, bilaterally.

Controls<MCI Retrieval. Only the premotor area was more activated in MCI persons than in healthy controls during the retrieval phase.

Correlational analyses

To perform correlational analyses, the average beta values of prefrontal and temporal clusters that were different between MCI and healthy controls were first extracted. Table 3 shows the mean beta values obtained for each group as well as the range of values for each area. Pearson correlations were then calculated between those values and the MDRS scores as a measure of disease severity in MCI. Pearson correlations were also calculated between those values and the performances of healthy controls and MCI to assess whether the activation of those regions were linked to enhanced performances and hence to possible compensatory mechanisms. Correlation coefficients and significance values are presented in Table 4. Strong positive correlations

were found in MCI between the activation of their right middle and superior temporal gyri at encoding and their scores on the MDRS ($r = .79$, $p < .001$, and $r = .55$, $p < .05$, respectively). In addition, there was a negative correlation between the activation of the right anterior cingulate and medial frontal cortex in MCI and their scores on the MDRS ($r = -.52$, $p < .05$) (see Figure 2). A positive correlation was also found in MCI between the activation of the left inferior frontal gyrus at encoding and their performances in the scanner ($r = .55$) (see Figure 3a). Importantly, there was no correlation between activation in the occipital areas and performance scores. In healthy controls, none of the correlations reached significance (see Table 4 and Figure 3b).

Discussion

The purpose of this study was to compare the brain activation patterns associated with verbal memory encoding and retrieval processes in MCI persons and healthy older adults and to assess its relation to disease severity and performance. Healthy older adults activated a brain network that included the lateral prefrontal cortex bilaterally, the lateral parietal cortex bilaterally, and the anterior cingulate cortex bilaterally. Globally, a similar network was activated during encoding and retrieval but smaller areas of activation were found in the prefrontal and mediotemporal cortex during retrieval. Previous studies indicate that in young adults, the left lateral prefrontal cortex is related to episodic memory encoding while the right lateral prefrontal cortex is related to episodic memory retrieval, (Hemispheric encoding/retrieval asymmetry in episodic memory, HERA model; Tulving et al., 1994). In the present study, activations were observed in the areas activated by younger adults with similar paradigms except that they were mostly bilateral in our group of healthy older adults. Interestingly, this finding of bilateral activation

during the encoding and retrieval phases in healthy older adults is consistent with numerous findings indicating reduced lateralization of prefrontal activity in older adults (Hemispheric asymmetry reduction in older adults, HAROLD model; Cabeza, 2002, 2001; Madden et al., 1999). Our finding of activation in the anterior cingulate cortex and in the lateral parietal lobe in verbal episodic memory is consistent with similar data that has also been reported in younger participants (see Cabeza and Nyberg, 2000, for a review). However, their exact contribution remains debatable when obtained in designs using rest with closed eyes as control condition as was done here, because they may also reflect attentional processes or phonological verbal memory. Overall, our paradigm was therefore successful in activating the brain regions that are typically reported to be involved in similar episodic memory tasks and also possibly those areas involved in sensory or attentional processes.

Our paradigm led to a number of differences in terms of brain activation between the MCI and control groups particularly at encoding. First, at encoding persons with MCI showed less activation than controls in the occipital lobe, in the thalamus, in the right anterior cingulate and medial frontal gyri as well as in the right middle and right superior temporal gyri. Considering that MCI is viewed as a prodrome of AD, our findings of hypoactivation of the posterior areas of the brain in MCI persons may appear surprising but are in fact consistent with the finding that the early phase BOLD response is significantly diminished in the occipital region of MCI patients compared to controls (Rombouts et al., 2005). This latter finding was interpreted as reflecting a combination of both a modification of the neurovascular coupling and diminished neuronal response in the occipital region. Similarly, the hypoactivation of the right middle and right superior

temporal gyri may result from the medial temporal lobe pathologies that hallmark early AD (Arnold et al., 1991; Braak and Braak, 1991; Markesbery et al., 2006; Mitchell et al., 2002). This is also coherent with PET studies showing a reduction of metabolism in AD in the right middle temporal (Kessler et al., 1991; Schroder et al., 2001) and superior temporal (Schroder et al., 2001) cortex. The PET study reported by Schroder and colleagues (2001) was done while participants completed a serial verbal learning task whereas the one reported by Kessler and colleagues (1991) was done using both resting state and a visual recognition task (i.e. recognition of black and white pictures of concrete objects, words or figures). Interestingly, both studies showed an association between increased disease severity in AD patients and larger reduction in metabolism.

In addition to the hypoactivations mentioned above, MCI participants showed more activation during encoding than healthy controls in the left inferior frontal gyrus (Brodmann's area 47). In the context of verbal episodic memory encoding, the role of this region has been attributed to semantic elaboration of verbal material (Demb et al., 1995; Poldrack et al., 1999). The finding of a greater activation of this region in MCI than in controls is not uncommon in conditions of matched performance. Similar findings have been found in a study of Rosano and colleagues (2005) who reported increased prefrontal cortex activation when MCI patients matched the performance of controls on an attention task, and in a study of Bookheimer and collaborators (2000) who also reported increased prefrontal cortex activation during matched memory task performance in high risk subjects. In turn, it is interesting to note that reduced activation has been found in the same region during the encoding of visual material in a study where healthy controls outperformed persons with MCI (Mandzia et al., 2007). Thus increased

prefrontal activation indicates compensatory activation when performance is matched whereas decreased activation associated with impaired performance indicates failed compensation in persons with MCI.

During retrieval, very few significant differences were found when the two groups were compared in spite of the fact that the extent of activations in MCI appears larger than the ones found in healthy controls. Statistically, the only significant difference was in fact that of a lower activation for MCI persons than healthy controls in the medial frontal gyrus bilaterally and of a larger activation in the left premotor area. This suggests either that the difference in activation between the two groups is small or that the activation associated with retrieval is characterized by important inter-subject variability. Be this as it may, our finding that retrieval elicits relatively small group differences between MCI and healthy controls supports previous studies reporting group differences circumscribed only to small brain areas during the retrieval phase (Mandzia et al., 2002; Mandzia et al., 2007; Heun et al., 2007; Ries et al., 2005).

One of our main goals was to investigate the effect of disease severity on the brain activation of MCI persons. We used impairment on a global neuropsychological scale, the MDRS, as an estimate of disease severity and found strong positive correlations between the MDRS and activation of the right middle and right superior temporal gyri of MCI persons ($r = .79$ and $r = .55$, respectively). Thus in MCI, the presence of increased cognitive deficits is associated with less activation in these areas. This is consistent with the presence of a gradual increase of neuropathologies in the temporal lobe during the MCI phase. The functional impact of these temporal lobe

pathologies could result in a decrease of activation in the neighborhood regions along with an increase in severity and clinical symptoms. In addition, a negative correlation was found between the MDRS and the activation of the right anterior cingulate cortex and of the medial prefrontal cortex (r = -.52). Thus, in MCI the presence of increased cognitive symptoms is associated with more activation in those areas. As the anterior cingulate cortex has been found to be more activated in tasks that have a high level of difficulty than in easier ones (Paus et al., 1998), this could reflect increased difficulty in MCI to perform the task as the disease progresses. Interestingly, a moderate positive association (r = .55) was found in persons with MCI between performance on the recognition task and activation of the left inferior frontal gyrus (Brodmann's area 47), a region that shows hyperactivation in MCI. A similar positive relationship between performance and brain activation has been linked to compensation mechanisms in healthy older adults (Cabeza et al., 2002). Our finding of an increased activation of this area in MCI and our finding that larger activation correlates with better performance is also reflective of compensatory mechanisms. This finding contrasts with a recent study of verbal episodic memory that found no correlation between performance and activation of the left ventrolateral prefrontal cortex in MCI (Brodmann's areas 44 and 45) (Dannhauser et al., 2008). There are many factors that could explain the difference in the Dannahauser's study and the present one. First, MCI individuals in Dannhauser's study (2008) were older (mean age of 72 vs 68 in our study) and might thus be more advanced into the disease. This is supported by the fact that persons with MCI in our study had milder impairment on the MMSE, an abbreviated cognitive measure (mean MMSE: 27.83), than those in Dannhauser et al. (2008) study (mean MMSE: 24.50). This is coherent with our hypothesis that only milder MCI rely on the compensatory neural

changes indexed by increased activation. Another possible account relates to task difficulty, as the task in the Dannhauser's study produced lower levels of performance (corrected recognition rate of 0.48 for healthy controls of 0.26 for MCIs) than the task used in our study, particularly for MCI persons (corrected recognition rate of 0.50 for controls and 0.42 for MCI). This might be due to the fact that word presentation was shorter in the Dannhauser's study (2.5 sec/word vs 4.0 sec/word in this study). A short presentation time might also have precluded initiation of compensation strategies in MCI.

The present study has some limitations. First, we used a low-level control task (rest) rather than a high-level control task and therefore the activation differences that we found between our groups could be related to the sensory, attentional, and/of working memory processing that supports and controls memory rather than to the encoding process. Note that the fact that we did not find a significant association between performances of MCI in the scanner and their occipital lobe activation diminishes the possibility of altered sensory processing as a significant factor in our MCI group. However, this possibility cannot be entirely ruled out because some studies have reported decreased attentional (Belleville et al, 2006; 2008) and sensory (Vannini et al., 2007) processing in MCI. To better control for the contribution of attention or sensory processing, future studies might use high-level control conditions that match the memory condition on every aspect apart from the encoding process. Another limitation of our study is the small sample size of healthy controls (N = 10) and of MCI individuals (N = 12). While this may have decreased our statistical power, it is important to note that we did nonetheless obtain a very coherent pattern of significant group effects in brain activation levels and significant correlations. Another limitation is that our task was

relatively easy and may have lacked the sensibility to distinguish MCIs from healthy controls. While absence of a group difference in performance greatly simplifies the interpretation of the group difference in cerebral activation (Gould et al., 2005), the lack of sensitivity could have overshadowed some potential cognitive compensation processes in either of the two groups. A potential compromise could be to use a parametric design with two or three conditions of different levels of difficulty. Lastly, we cannot rule out the possibility that some of the subjects might have been doing something other than memorizing the words during memory encoding as no online measure of behavior was taken. However, we are comforted by the fact that both MCI individuals and healthy controls performed above chance in the task and by the fact that our subjects showed activation in regions that are commonly activated in fMRI memory taks (i.e. ventrolateral and dorsolateral prefrontal cortices and medial temporal lobe).

To conclude, findings of this study indicate that MCI individuals and healthy older adults show brain activations differences particularly during the encoding phase of verbal episodic memory and relatively fewer brain activation differences during the retrieval phase. During encoding, MCI persons show hypoactivation of the right middle and superior temporal gyri, a region that has been shown to be structurally compromised and that is known to show hypometabolism in AD. Our finding may thus reflect a very early involvement of those areas during the MCI phase. Importantly, reduced activation in the right middle and superior temporal gyri was strongly associated with disease severity, as measured with the MDRS indicating that reduced activation increases with the disease. In contrast, hyperactivation in the left ventrolateral prefrontal cortex was observed in MCI persons. This increased activation correlated with the MCIs'

performance on the memory task and could thus represent compensatory mechanisms, possibly in response to the hypoactivation of the temporal network. These compensatory mechanisms could be cognitive for example, patients could be using alternative cognitive strategies to perform the tasks (e.g.: greater reliance on rehearsal or semantic elaboration attempt). They might also be strictly neuronal, that is, reflecting changes in the neural architecture due to neural change (e.g.: increased activation of contralateral regions), or both (see Cabeza, 2002). Future studies will be necessary to assess the relative contribution of cognitive and neuronal compensation and whether this prefrontal compensatory activation can be enhanced, either with pharmacological or non-pharmacological interventions.

Footnotes

1. Note that the performances of two MCI persons were not recorded due to equipment failure.

References

ARNOLD SE, HYMAN BT, FLORY J, DAMASIO AR, and VAN HOESEN GW. The topographical and neuroanatomical distribution of neurofibrillary tangles and neuritic plaques in the cerebral cortex of patients with alzheimer's disease. *Cereb Cortex,* 1: 103-16, 1991.

AULD DS, KORNECOOK TJ, BASTIANETTO S, and QUIRION R. Alzheimer's disease and the basal forebrain cholinergic system: Relations to beta-amyloid peptides, cognition, and treatment strategies. *Prog Neurobiol,* 68: 209-45, 2002.

BENNETT DA, WILSON RS, SCHNEIDER JA, EVANS DA, BECKETT LA, AGGARWAL NT, BARNES LL, FOX JH, and BACH J. Natural history of mild cognitive impairment in older persons. *Neurology,* 59: 198-205, 2002.

BENTON AL, HAMSHER K, VARNEY NR, and SPREEN O. *Contributions to neuropsychological assessment*. New York: Oxford University Press, 1983.

BONDI MW, HOUSTON WS, EYLER LT, and BROWN GG. Fmri evidence of compensatory mechanisms in older adults at genetic risk for alzheimer disease. *Neurology,* 64: 501-8, 2005.

BOOKHEIMER SY, STROJWAS MH, COHEN MS, SAUNDERS AM, PERICAK-VANCE MA, MAZZIOTTA JC, and SMALL GW. Patterns of brain activation in people at risk for alzheimer's disease. *N Engl J Med,* 343: 450-6, 2000.

BRAAK H and BRAAK E. Neuropathological stageing of alzheimer-related changes. *Acta Neuropathol (Berl),* 82: 239-59, 1991.

BRETT M, ANTON J-L, VALABREGUE R, and POLINE J-P. *Region of interest analysis using an spm toolbox Secondary Titl*. Sendai, Japan. Available on CD-ROM in NeuroImage, Vol 16, No 2., 2002.

BUSCHKE H. Cued recall in amnesia. *Journal of Clinical Neuropsychology,* 6: 433-440, 1984.

CABEZA R. Cognitive neuroscience of aging: Contributions of functional neuroimaging. *Scand J Psychol,* 42: 277-86, 2001.

CABEZA R. Hemispheric asymmetry reduction in older adults: The harold model. *Psychol Aging,* 17: 85-100, 2002.

CABEZA R, ANDERSON ND, LOCANTORE JK, and MCINTOSH AR. Aging gracefully: Compensatory brain activity in high-performing older adults. *Neuroimage,* 17: 1394-1402, 2002.

CABEZA R and NYBERG L. Imaging cognition ii: An empirical review of 275 pet and fmri studies. *J Cogn Neurosci,* 12: 1-47, 2000.

CABEZA R. Hemispheric asymmetry reduction in older adults: The harold model. *Psychol Aging,* 17: 85-100, 2002.

CELONE KA, CALHOUN VD, DICKERSON BC, ATRI A, CHUA EF, MILLER SL, DEPEAU K, RENTZ DM, SELKOE DJ, BLACKER D, ALBERT MS, and SPERLING RA. Alterations in memory networks in mild cognitive impairment and alzheimer's disease: An independent component analysis. *J Neurosci,* 26: 10222-31, 2006.

CHETELAT G, EUSTACHE F, VIADER F, DE LA SAYETTE V, PELERIN A, MEZENGE F, HANNEQUIN D, DUPUY B, BARON JC, and DESGRANGES B. Fdg-pet measurement is more accurate than neuropsychological assessments to predict global cognitive deterioration in patients with mild cognitive impairment. *Neurocase,* 11: 14-25, 2005.

CLEMENT F, BELLEVILLE S, and GAUTHIER S. Cognitive complaint in mild cognitive impairment and alzheimer's disease. *J Int Neuropsychol Soc,* 14: 222-32, 2008.

DANNHAUSER TM, SHERGILL SS, STEVENS T, LEE L, SEAL M, WALKER RW, and WALKER Z. An fmri study of verbal episodic memory encoding in amnestic mild cognitive impairment. *Cortex,* 44: 869-80, 2008.

DEMB JB, DESMOND JE, WAGNER AD, VAIDYA CJ, GLOVER GH, and GABRIELI JD. Semantic encoding and retrieval in the left inferior prefrontal cortex: A functional mri study of task difficulty and process specificity. *J Neurosci,* 15: 5870-8, 1995.

DESROSIERS J, BRAVO G, HEBERT R, and DUBUC N. Reliability of the revised functional autonomy measurement system (smaf) for epidemiological research. *Age Ageing,* 24: 402-6, 1995.

DICKERSON BC, SALAT DH, GREVE DN, CHUA EF, RAND-GIOVANNETTI E, RENTZ DM, BERTRAM L, MULLIN K, TANZI RE, BLACKER D, ALBERT MS, and SPERLING RA. Increased hippocampal activation in mild cognitive impairment compared to normal aging and ad. *Neurology,* 65: 404-11, 2005.

ERTEN-LYONS D, HOWIESON D, MOORE MM, QUINN J, SEXTON G, SILBERT L, and KAYE J. Brain volume loss in mci predicts dementia. *Neurology,* 66: 233-5, 2006.

FOLSTEIN MF, FOLSTEIN SE, and MCHUGH PR. Mini-mental state: A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research,* 12: 189-198, 1975.

FURIO AM, BRUSCO LI, and CARDINALI DP. Possible therapeutic value of melatonin in mild cognitive impairment: A retrospective study. *J Pineal Res,* 43: 404-9, 2007.

GARDNER R, JR., OLIVER-MUNOZ S, FISHER L, and EMPTING L. Mattis dementia rating scale: Internal reliability study using a diffusely impaired population. *J Clin Neuropsychol,* 3: 271-5, 1981.

GAUTHIER S, REISBERG B, ZAUDIG M, PETERSEN RC, RITCHIE K, BROICH K, BELLEVILLE S, BRODATY H, BENNETT D, CHERTKOW H, CUMMINGS JL, DE LEON M, FELDMAN H, GANGULI M, HAMPEL H, SCHELTENS P, TIERNEY MC, WHITEHOUSE P, and WINBLAD B. Mild cognitive impairment. *Lancet,* 367: 1262-70, 2006.

GOULD RL, BROWN RG, OWEN AM, BULLMORE ET, WILLIAMS SC, and HOWARD RJ. Functional neuroanatomy of successful paired associate learning in alzheimer's disease. *Am J Psychiatry,* 162: 2049-60, 2005.

GRAFF-RADFORD NR, CROOK JE, LUCAS J, BOEVE BF, KNOPMAN DS, IVNIK RJ, SMITH GE, YOUNKIN LH, PETERSEN RC, and YOUNKIN SG. Association of low plasma abeta42/abeta40 ratios with increased imminent risk for mild cognitive impairment and alzheimer disease. *Arch Neurol,* 64: 354-62, 2007.

HAMALAINEN A, PIHLAJAMAKI M, TANILA H, HANNINEN T, NISKANEN E, TERVO S, KARJALAINEN PA, VANNINEN RL, and SOININEN H. Increased fmri responses during encoding in mild cognitive impairment. *Neurobiol Aging,* 28: 1889-903, 2007.

HAN SD, HOUSTON WS, JAK AJ, EYLER LT, NAGEL BJ, FLEISHER AS, BROWN GG, COREY-BLOOM J, SALMON DP, THAL LJ, and BONDI MW. Verbal paired-associate learning by apoe genotype in non-demented older adults: Fmri evidence of a right hemispheric compensatory response. *Neurobiol Aging*, 2006.

HEUN R, FREYMANN K, ERB M, LEUBE DT, JESSEN F, KIRCHER TT, and GRODD W. Mild cognitive impairment (mci) and actual retrieval performance affect cerebral activation in the elderly. *Neurobiol Aging,* 28: 404-13, 2007.

JACK CR, JR., PETERSEN RC, XU YC, O'BRIEN PC, SMITH GE, IVNIK RJ, BOEVE BF, WARING SC, TANGALOS EG, and KOKMEN E. Prediction of ad with mri-based

hippocampal volume in mild cognitive impairment. *Neurology,* 52: 1397-403, 1999.

JOHNSON SC, SCHMITZ TW, MORITZ CH, MEYERAND ME, ROWLEY HA, ALEXANDER AL, HANSEN KW, GLEASON CE, CARLSSON CM, RIES ML, ASTHANA S, CHEN K, REIMAN EM, and ALEXANDER GE. Activation of brain regions vulnerable to alzheimer's disease: The effect of mild cognitive impairment. *Neurobiol Aging,* 27: 1604-12, 2006.

KAPLAN EF, GOODGLASS H, and WEINTRAUB S. *The boston naming test (2nd edition)*. Philadelphia, PA: Lea & Febiger, 1983.

KESSLER J, HERHOLZ K, GROND M, and HEISS WD. Impaired metabolic activation in alzheimer's disease: A pet study during continuous visual recognition. *Neuropsychologia,* 29: 229-43, 1991.

KIRCHER T, WEIS S, FREYMANN K, ERB M, JESSEN F, GRODD W, HEUN R, and LEUBE DT. Hippocampal activation in mci patients is necessary for successful memory encoding. *J Neurol Neurosurg Psychiatry,* 78: 812-8, 2007.

KORF ES, WAHLUND LO, VISSER PJ, and SCHELTENS P. Medial temporal lobe atrophy on mri predicts dementia in patients with mild cognitive impairment. *Neurology,* 63: 94-100, 2004.

MACHULDA MM, WARD HA, BOROWSKI B, GUNTER JL, CHA RH, O'BRIEN PC, PETERSEN RC, BOEVE BF, KNOPMAN D, TANG-WAI DF, IVNIK RJ, SMITH GE, TANGALOS EG, and JACK CR, JR. Comparison of memory fmri response among normal, mci, and alzheimer's patients. *Neurology,* 61: 500-6, 2003.

MADDEN DJ, TURKINGTON TG, PROVENZALE JM, DENNY LL, HAWK TC, GOTTLOB LR, and COLEMAN RE. Adult age differences in the functional neuroanatomy of verbal recognition memory. *Hum Brain Mapp,* 7: 115-35, 1999.

MANDZIA J, BLACK S, GRADY C, MCANDREWS MP, and GRAHAM S. Encoding and retrieval in aging and memory loss, a fmri study. *Brain Cogn,* 49: 225-8, 2002.

MANDZIA JL, MCANDREWS MP, GRADY CL, GRAHAM SJ, and BLACK SE. Neural correlates of incidental memory in mild cognitive impairment: An fmri study. *Neurobiol Aging,* doi:10.1016/j.neurobiolaging.2007.08.024, 2007.

MARKESBERY WR, SCHMITT FA, KRYSCIO RJ, DAVIS DG, SMITH CD, and WEKSTEIN DR. Neuropathologic substrate of mild cognitive impairment. *Arch Neurol,* 63: 38-46, 2006.

MATTIS S. Mental status examination for organic mental syndrome in the elderly patient. In Bellak L. and Karasu T.B. (Eds.), *Geriatric psychiatry*. New York: Grune & Stratton, 1976.

MESULAM M, SHAW P, MASH D, and WEINTRAUB S. Cholinergic nucleus basalis tauopathy emerges early in the aging-mci-ad continuum. *Ann Neurol,* 55: 815-28, 2004.

MITCHELL TW, MUFSON EJ, SCHNEIDER JA, COCHRAN EJ, NISSANOV J, HAN LY, BIENIAS JL, LEE VM, TROJANOWSKI JQ, BENNETT DA, and ARNOLD SE. Parahippocampal tau pathology in healthy aging, mild cognitive impairment, and early alzheimer's disease. *Ann Neurol,* 51: 182-9, 2002.

PAUS T, KOSKI L, CARAMANOS Z, and WESTBURY C. Regional differences in the effects of task difficulty and motor output on blood flow response in the human anterior

cingulate cortex: A review of 107 pet activation studies. *Neuroreport,* 9: R37-47, 1998.

PENNANEN C, KIVIPELTO M, TUOMAINEN S, HARTIKAINEN P, HANNINEN T, LAAKSO MP, HALLIKAINEN M, VANHANEN M, NISSINEN A, HELKALA EL, VAINIO P, VANNINEN R, PARTANEN K, and SOININEN H. Hippocampus and entorhinal cortex in mild cognitive impairment and early ad. *Neurobiol Aging,* 25: 303-10, 2004.

PENNANEN C, TESTA C, LAAKSO MP, HALLIKAINEN M, HELKALA EL, HANNINEN T, KIVIPELTO M, KONONEN M, NISSINEN A, TERVO S, VANHANEN M, VANNINEN R, FRISONI GB, and SOININEN H. A voxel based morphometry study on mild cognitive impairment. *J Neurol Neurosurg Psychiatry,* 76: 11-4, 2005.

PETERSEN RC, DOODY R, KURZ A, MOHS RC, MORRIS JC, RABINS PV, RITCHIE K, ROSSOR M, THAL L, and WINBLAD B. Current concepts in mild cognitive impairment. *Arch Neurol,* 58: 1985-92, 2001.

PETRELLA JR, WANG L, KRISHNAN S, SLAVIN MJ, PRINCE SE, TRAN TT, and DORAISWAMY PM. Cortical deactivation in mild cognitive impairment: High-field-strength functional mr imaging. *Radiology,* 245: 224-35, 2007.

POLDRACK RA, WAGNER AD, PRULL MW, DESMOND JE, GLOVER GH, and GABRIELI JD. Functional specialization for semantic and phonological processing in the left inferior prefrontal cortex. *Neuroimage,* 10: 15-35, 1999.

PRVULOVIC D, VAN DE VEN V, SACK AT, MAURER K, and LINDEN DE. Functional activation imaging in aging and dementia. *Psychiatry Res,* 140: 97-113, 2005.

REGARD M. *Cognitive rigidity and flexibility: A neuropsychological study*. *Secondary Titl*.: University of Victoria, Canada, 1981.

REY A. *Test de copie d'une figure complexe: Manuel*. Paris: Les éditions du centre de psychologie appliquée, 1959.

RIES ML, SCHMITZ TW, KAWAHARA TN, TORGERSON BM, TRIVEDI MA, and JOHNSON SC. Task-dependent posterior cingulate activation in mild cognitive impairment. *Neuroimage,* 29: 485-92, 2005.

ROMBOUTS SA, GOEKOOP R, STAM CJ, BARKHOF F, and SCHELTENS P. Delayed rather than decreased bold response as a marker for early alzheimer's disease. *Neuroimage,* 26: 1078-85, 2005.

ROSANO C, AIZENSTEIN HJ, COCHRAN JL, SAXTON JA, DE KOSKY ST, NEWMAN AB, KULLER LH, LOPEZ OL, and CARTER CS. Event-related functional magnetic resonance imaging investigation of executive control in very old individuals with mild cognitive impairment. *Biol Psychiatry,* 57: 761-7, 2005.

SCHRODER J, BUCHSBAUM MS, SHIHABUDDIN L, TANG C, WEI TC, SPIEGEL-COHEN J, HAZLETT EA, ABEL L, LUU-HSIA C, CIARAVOLO TM, MARIN D, and DAVIS KL. Patterns of cortical activity and memory performance in alzheimer's disease. *Biol Psychiatry,* 49: 426-36, 2001.

SIGNORET JL. *Batterie d'efficience mnésique bem 144*. Paris: Elsevier, 1991.

TULVING E, KAPUR S, CRAIK FI, MOSCOVITCH M, and HOULE S. Hemispheric encoding/retrieval asymmetry in episodic memory: Positron emission tomography findings. *Proc Natl Acad Sci U S A,* 91: 2016-20, 1994.

TRIVEDI MA, SCHMITZ TW, RIES ML, TORGERSON BM, SAGER MA, HERMANN BP, ASTHANA S, and JOHNSON SC. Reduced hippocampal activation during episodic encoding in middle-aged individuals at genetic risk of alzheimer's disease: A cross-sectional study. *BMC Med,* 4: 1, 2006.

VAN DER LINDEN M, ADAM S, AGNIEL A, BAISSET-MOULY C, BARDET F, COYETTE F, DESGRANGES B, DEWEER B, ERGIS AM, GÉLY-NARGEOT MC, GRIMOMPREZ L, JUILLERAT AC, KALAFAT M, POITRENAUD J, SELLAL F, and THOMAS-ANTÉRION C. *L'évaluation de troubles de la mémoire: Présentation de quatre tests de mémoire épisodique (avec étalonnage)*. Marseille: Solal, 2004.

VANNINI P, ALMKVIST O, DIERKS T, LEHMANN C, and WAHLUND LO. Reduced neuronal efficacy in progressive mild cognitive impairment: A prospective fmri study on visuospatial processing. *Psychiatry Res,* 156: 43-57, 2007.

WAGNER AD, SCHACTER DL, ROTTE M, KOUTSTAAL W, MARIL A, DALE AM, ROSEN BR, and BUCKNER RL. Building memories: Remembering and forgetting of verbal experiences as predicted by brain activity. *Science,* 281: 1188-91, 1998.

WECHSLER D. *Wechsler adult intelligence scale-iii* New York: Psychological Corporation, 1997.

WHITWELL JL, PRZYBELSKI SA, WEIGAND SD, KNOPMAN DS, BOEVE BF, PETERSEN RC, and JACK CR, JR. 3d maps from multiple mri illustrate changing atrophy patterns as subjects progress from mild cognitive impairment to alzheimer's disease. *Brain,* 130: 1777-86, 2007.

WINBLAD B, PALMER K, KIVIPELTO M, JELIC V, FRATIGLIONI L, WAHLUND LO, NORDBERG A, BACKMAN L, ALBERT M, ALMKVIST O, ARAI H, BASUN H, BLENNOW K, DE LEON M, DECARLI C, ERKINJUNTTI T, GIACOBINI E, GRAFF C, HARDY J, JACK C, JORM A, RITCHIE K, VAN DUIJN C, VISSER P, and PETERSEN RC. Mild cognitive impairment--beyond controversies, towards a consensus: Report of the international working group on mild cognitive impairment. *J Intern Med,* 256: 240-6, 2004.

XU Y, JACK CR, JR., O'BRIEN PC, KOKMEN E, SMITH GE, IVNIK RJ, BOEVE BF, TANGALOS RG, and PETERSEN RC. Usefulness of mri measures of entorhinal cortex versus hippocampus in ad. *Neurology,* 54: 1760-7, 2000.

Acknowledgement

This work was supported in part by a grant from the FRSQ Repar and Repric and by a grant from CIHR to SB. SB receives an FRSQ chercheur-national. FC was supported by a scholarship from CIHR. We thank Luke Henry and Ellen Moscoe for editorial assistance. The authors have reported no conflicts of interest.

Table 1.

Scores on the neuropsychological tasks for the two groups. SD is in parenthesis.

	Controls n = 10	MCI n = 12
MDRS	140.40 (3.10)	133.83 (8.03) *
MMSE	29.10 (.74)	27.83 (1.59) *
RL/RI-16 3rd free recall	12.20 (1.87)	7.33 (4.54) **
RL/RI-16 delayed free recall	13.50 (1.18)	8.17 (4.13) **

Note. Significant impairment relative to controls, * $p < .05$; ** at $p < .01$

Table 2

Clusters (>10 voxels) significantly more activated in healthy controls than in MCI persons or significantly more activated in MCI persons than in healthy controls with cluster size, peak voxel coordinates and corresponding t-values.

Activates areas (Brodmann area) ($p < .005$)	Cluster Size	x	y	z	t value
CA > MCI Encoding					
Left occipital lobe (BA 18/19)	82	-27	-90	0	5.18
Right occipital lobe (BA 18/19)	146	27	-81	18	4.13
Right anterior cingulate/medial frontal gyri	29	3	54	12	3.68
Right thalamus	13	15	-12	3	3.66
Right middle temporal gyrus (BA 21)	12	60	-21	14	3.31
Right superior temporal gyrus (BA 22)	14	45	-21	-9	3.04
CA < MCI Encoding					
Left inferior frontal gyrus (BA 47)	29	-48	27	-6	3.56
CA > MCI Retrieval					
Right/left medial frontal gyrus (BA 10)	28	0	54	12	3.80
CA < MCI Retrieval					
Left premotor area (BA 6)	12	-15	-6	72	3.54

Table 3.

Mean average beta values of clusters that are different between the two groups. Range of values is in parenthesis.

Activates areas (Brodmann area) ($p < .005$)	MCIs	Controls
CA > MCI Encoding		
Left occipital lobe (BA 18/19)	.61 (-0.86 – 2.12)	2.08 (.74 – 3.42)
Right occipital lobe (BA 18/19)	.51 (-.96 – 2.25)	1.84 (1.01 – 3.48)
Right anterior cingulate/ medial frontal gyri	.34 (-1.34 – .99)	.79 (-.15 – 1.49)
Right middle temporal gyrus (BA 21)	-.47 (-1.09 – .12)	.17 (-.46 – .77)
Right superior temporal gyrus (BA 22)	-.72 (-2.16 – -.16)	.32 (-.63 – 1.15)
CA < MCI Encoding		
Left inferior frontal gyrus (BA 47)	.82 (.06 – 2.28)	-.28 (-1.27 – .47)
CA > MCI Retrieval		
Right/left medial frontal gyrus (BA 10)	.52 (-.72 – 1.66)	.56 (-.56 – 2.15)
CA < MCI Retrieval		
Left premotor area (BA 6)	-.32 (-1.50 – 0.72)	-.66 (-.1.42 – -.17)

Table 4.

Correlations between average beta values of clusters that are different between the two groups with performance scores of controls and MCIs and with MDRS scores of MCIs.

Activates areas (Brodmann area)	Performances		MDRS
(p < .005)	MCIs	Controls	MCIs
CA > MCI Encoding			
Left occipital lobe (BA 18/19)	.33	.13	-.16
Right occipital lobe (BA 18/19)	.36	-.01	.13
Right anterior cingulate & medial frontal gyri	.15	.13	-.52 *
Right middle temporal gyrus (BA 21)	.31	.17	.79 **
Right superior temporal gyrus (BA 22)	.34	.14	.55 *
CA < MCI Encoding			
Left inferior frontal gyrus (BA 47)	.55 *	-.12	-.12
CA > MCI Retrieval			
Right/left medial frontal gyrus (BA 10)	.28	.17	-.30
CA < MCI Retrieval			
Left premotor area (BA 6)	.16	.21	-.18

Note. Significant impairment relative to controls, * p < .05; ** at p < .001

Figure Caption

Figure 1. Cerebral activations ($p < .001$, uncorrected, cluster size > 10) of healthy controls during encoding (a) and retrieval (b) and of MCI persons during encoding (c) and retrieval (d).

Figure 2. Scatter plots with fit lines showing the significant correlations in MCI between the scores on the MDRS and their beta values in a) the right middle temporal gyrus (BA 21) b) the right superior temporal gyrus (BA 22) and c) the right anterior cingulate & medial frontal gyri.

Figure 3. Scatter plots with fit lines showing the significant correlations between performances in the scanner and beta values for MCIs and healthy controls in the left inferior frontal gyrus (BA 47) (a and b respectively). Note that the correlations are only significant for MCIs.

Figure 1. Cerebral activations ($p < .001$, uncorrected, cluster size > 10) of healthy controls during encoding (a) and retrieval (b) and of MCI persons during encoding (c) and retrieval (d).

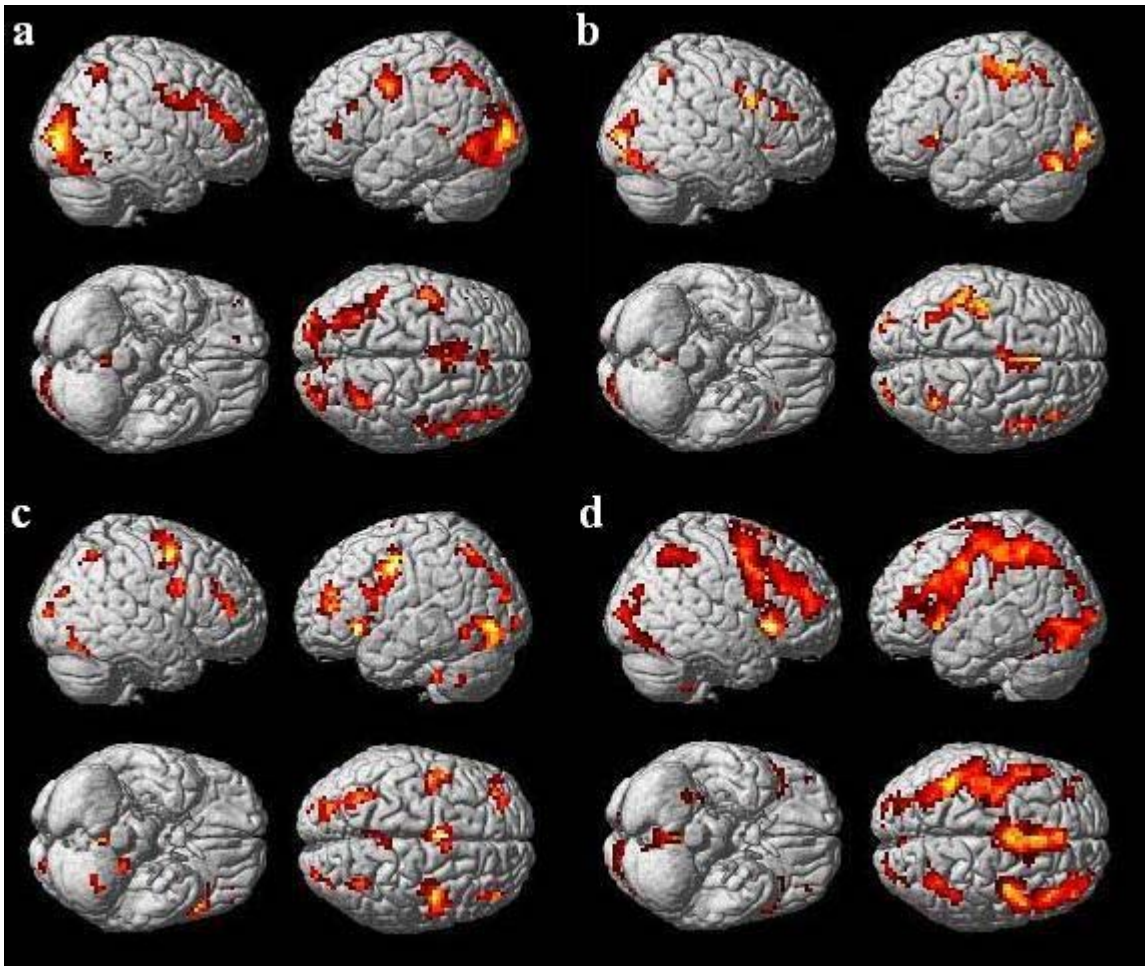


Figure 2. Scatter plots with fit lines showing the significant correlations in MCI between the scores on the MDRS and their beta values in a) the right middle temporal gyrus (BA 21) b) the right superior temporal gyrus (BA 22) and c) the right anterior cingulate & medial frontal gyri.

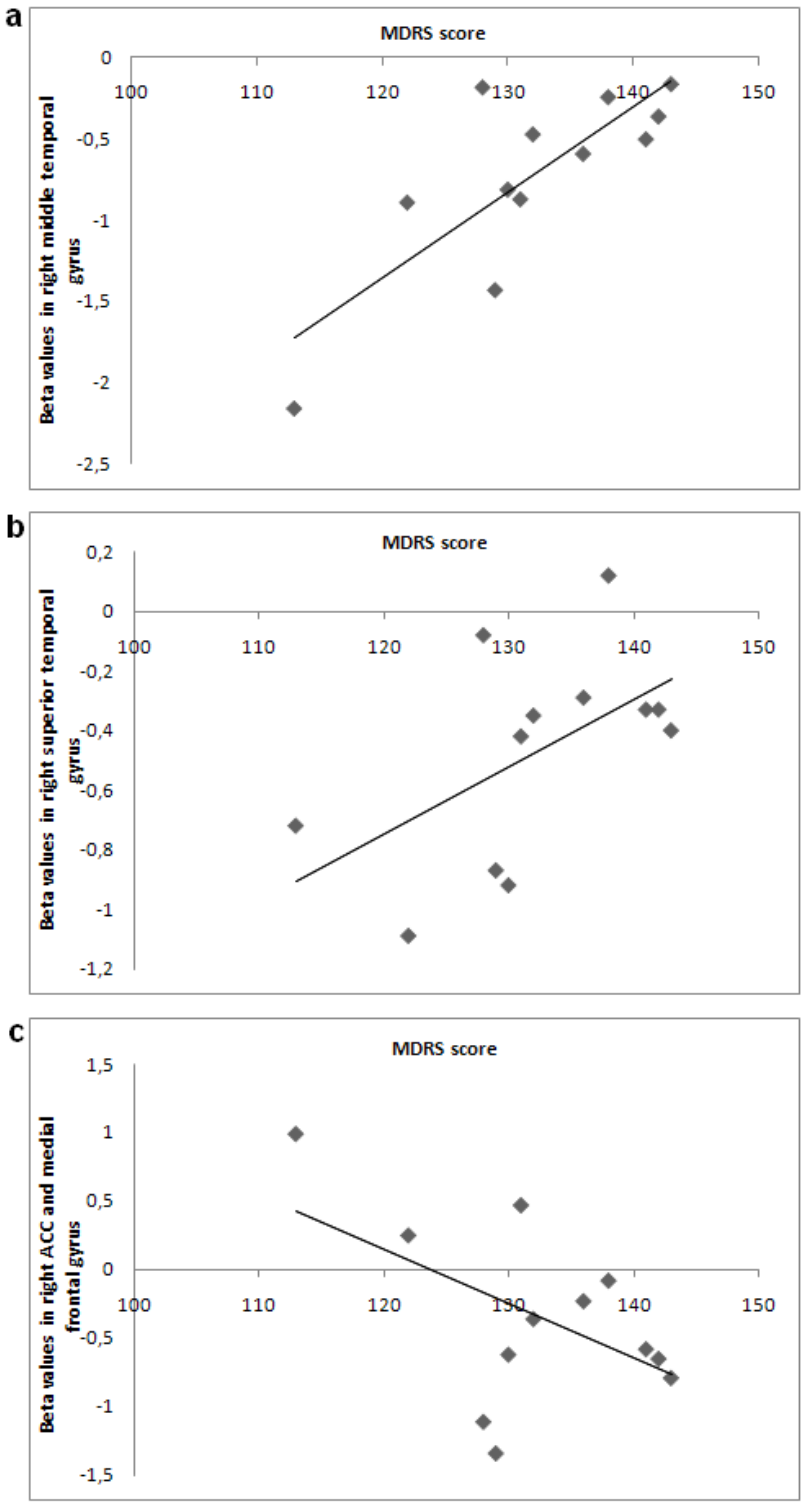
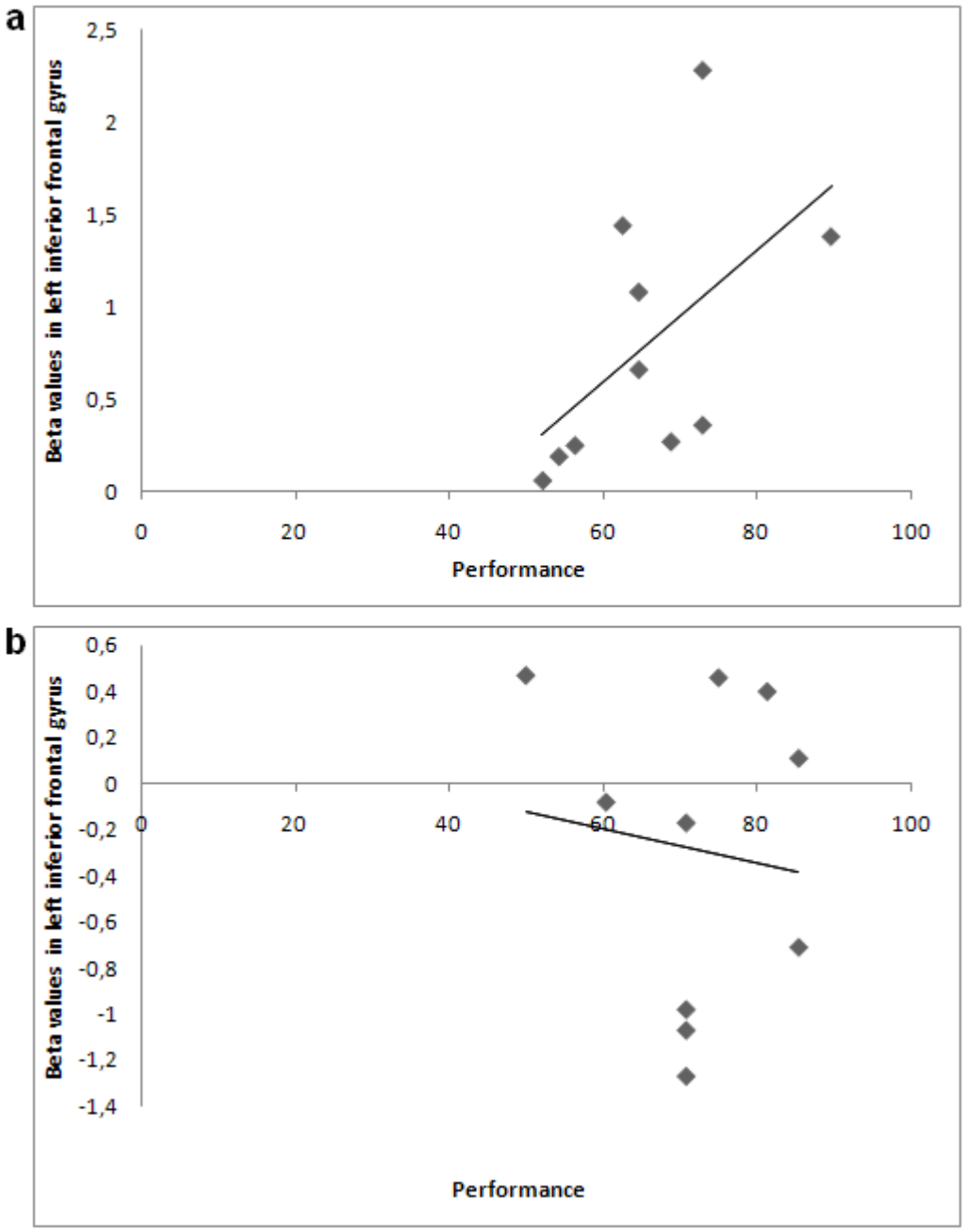


Figure 3. Scatter plots with fit lines showing the significant correlations between performances in the scanner and beta values in the left inferior frontal gyrus (BA 47) (a and b respectively) a) for MCI participants and b) for healthy controls. Note that the correlations are only significant for MCIs.



CHAPITRE 4

Article n° 3

Compensation and disease severity on the memory-related activations in mild cognitive impairment

Francis Clément & Sylvie Belleville

Biological psychiatry 2010; 68(10) : 894-902.

Abstract

Background: Alzheimer's disease (AD) is a neurodegenerative disease with progressive cognitive impairments that are likely to affect the compensatory mechanisms and the cerebral activation patterns of the patients. **Methods**: Functional neuroimaging was used to test the effect of disease severity on the brain activation of persons at risk for AD and to highlight the process of compensation in some of these individuals. This was done for the verbal learning of either semantically related or semantically unrelated word pairs. Twenty-six persons with mild cognitive impairment (MCI) were separated into two groups, MCI higher-cognition and MCI lower-cognition, using a split-median on their scores for the Mattis Dementia Rating Scale. A group of 14 healthy older adults were matched to the MCI participants. **Results**: In both task conditions, MCI higher-cognition activated additional regions, relative to controls, in the right ventrolateral and dorsolateral prefrontal brain areas. Additional areas of hyperactivation were found in the right prefrontal area 45 when encoding semantically related word pairs and in the left hippocampus during encoding of unrelated word pairs. In contrast, MCI lower-cognition failed to show additional prefrontal activations when compared to healthy controls, and showed decreased activation in posterior areas. **Conclusions**: These results are in line with compensation occurring at the beginning of the MCI continuum and with the breakdown of compensation in patients experiencing more severe symptoms.

Introduction

Alzheimer's disease (AD) is the most prevalent form of dementia. Neuroimaging activation techniques have been important in understanding how the disease impacts the neural circuitry that underlies cognitive functioning and compensation. However, despite the fact that AD is a progressive disorder, little is known about the effect of disease severity on the pattern of brain activation in AD (but see 1). In addition, progression through the disease continuum is likely to be marked by a compensation breakdown after a certain accumulation of lesions. The goal of this study is to assess the neural circuitry that allows some of the MCI individuals to retain capacities to compensate for their memory impairments.

Older persons with mild cognitive impairment do not meet criteria for dementia but many of them probably stand in a prodromal phase of the disease. Studies on the natural history of MCI indicate that there is a gradual increase in their symptom severity which likely parallels the accumulation of the underlying AD neuropathology (2). Degeneration models propose that there is a trade-off between the accumulation of lesions and the ability for the neural system to exhibit compensation (3, 4). It was proposed that neurodegenerative diseases that implicate a small amount of cerebral lesions would decrease processing efficiency but preserve processing capacity. This would allow increased recruitment of neurons to compensate for neuronal loss and prevent performance from decreasing. As more important neuronal damage accumulates, both processing efficiency and capacity would decrease. This would impede the capacity

for neuronal recruitment, reduce compensation capacities and result in a decreased level of performance (5, 6).

These models underscore the tremendous impact that disease severity is likely to bear on the expected pattern of brain activation in MCI and AD. Because persons with MCI first suffer from a relatively small amount of neural damage, the model would predict that those MCIs, at the beginning of the continuum to AD, would be able to activate compensatory networks in response to neural damage. This would result in increased functional activation, relative to healthy controls, in order to maintain relatively good levels of performance. This pattern would revert as persons with MCI suffer from more severe neural damage, which would be reflected in reduced brain activation and compensation breakdown associated with impaired performance level. The model also predicts that these changes in brain activation should be found mainly in AD-related brain areas as these regions are the ones that suffer from neural damage. There is data that seems to suggest that this might be the case in MCI (7, 8).

The effect of disease severity might reconcile some of the incompatibilities found in the literature on MCI. For instance, some studies reported decreased activation in the hippocampus and prefrontal cortex of MCI persons relative to healthy older adults (9, 10, 14-16) while others have reported increased activation (11-13). The hypothesis of a brain-related breakdown in neural compensation is also coherent with the data indicating that AD is characterized by reduced brain activation. However, the effect of disease severity has not been assessed directly in a single study that uses a common measure to assess severity across patients.

The goal of this study was to assess the impact of disease severity and of task characteristics on the memory-related brain activation of persons with MCI with the use of a verbal episodic memory encoding task. MCI persons were split into two groups as a function of their level of cognitive impairment on a dementia rating scale. The fMRI task included two encoding conditions: one that involved semantically related word pairs and one that involved unrelated word pairs. We hypothesized that MCIs with better cognitive functions (MCI higher-cognition) would be much less impaired than those with lower cognitive functions and would show additional activation in alternative structures or networks compared to healthy controls. In contrast, we hypothesized that MCIs with lesser cognitive functions (MCI lower-cognition) would be impaired on the task and would not show, or would show minimal, additional activations. Importantly, we hypothesized that most changes in brain activation would be found in AD-related brain areas. Finally, we also predicted that compensatory activations would be task-dependent.

Methods and Materials

Participants

Twenty-eight persons with MCI (17 females/11 males) and 14 healthy older adults (8 females/6 males) were initially recruited to take part in this study. Two of the MCI individuals (2 females/0 male) were excluded because they showed head movement in the scanner. French was the first language of all participants. Sociodemographic characteristics of the two groups are shown in Table 1.

MCI participants were referred from memory clinics and met the criteria proposed by Petersen (17-19) for amnestic single or multiple domain MCI (Supplement

1). Persons with MCI completed an extensive neuropsychological evaluation that covered episodic memory (Rappels libres/Rappels indices; RL/RI-16 free and cued word recall task, 21, 22, Batterie d'Efficience Mnésique; BEM text memory, 23, 20-min recall of the Rey's Complex Figure, 24), executive functions (third plate of Stroop-Victoria, 25, and copy of Rey's Complex Figure, 24), visuospatial processing (Benton Judgment of line orientation, 26), speed of information processing (Coding of the WAIS-III, 27), language (Modified Boston Naming Test, 28), and global cognitive functions (Mattis Dementia Rating Scale, MDRS, 29, and MMSE, 30). MCI persons also went through an extensive medical, neurological and neuroradiological examination to exclude the presence of any other significant systemic, neurological or psychiatric conditions that could explain their cognitive difficulties.

To assess the effect of disease severity on functional neuroimaging data, MCI participants were divided into two groups of different levels of cognitive impairment (MCI higher-cognition and MCI lower-cognition) using a split-median of their scores on the MDRS. The MDRS is an abbreviated neuropsychological scale that covers a wide range of cognitive functions. It therefore has the advantage of measuring severity independently of the episodic memory task used for the functional neuroimaging. Furthermore, it is more sensitive than the MMSE to MCI's quite subtle cognitive impairments. It also yields the variability necessary for the use of a split-median and is not curtailed by ceiling effects. See Supplement 1 for details on the follow-up of MCI participants.

Healthy older adults were recruited from the community and underwent a brief clinical and neuropsychological assessment to ensure that they did not suffer from cognitive deficits. The tasks included measures of global cognitive functions (MDRS[2], MMSE, Montreal Cognitive Assessment, MOCA; 31), speed of information processing (Coding), and episodic memory (RL/RI-16).

This study was approved by the Institut Universitaire de Gériatrie de Montréal Human Ethics (comité conjoint d'évaluation scientifique, CÉS-RNQ).

Task and fMRI procedures

Encoding was measured by asking participants to memorize 16 lists of nine pairs of concrete, one- or two-syllable, words. Half of the lists was composed of semantically related pairs of words (ex: butter-cheese) and the other half was composed of semantically unrelated pairs (ex: tea-bed). Related pairs were created by selecting an item and one of its associates from French lists of semantic associates (32, 33). To avoid guessing and to avoid that the two words get encoded as a single concept, only the words' second, third, or fourth associates were used. Lists of unrelated word pairs were created by selecting pairs of words with no semantic relation, ensuring that none were semantically associated with other items in the list. All sixteen lists were matched in terms of word frequency and word length. The task was programmed on E-prime. Word pairs were presented visually at a rate of 4 sec (seconds) per pair and were mirror-projected. Encoding was recorded in two runs. Each run included eight blocks of visual fixation (20 sec each), eight blocks of intentional encoding (one list per block, total of 40

[2] Five healthy controls did not complete the MDRS.

sec each) and eight blocks of recognition (40 sec each, see below). The order of presentation of the semantically related and unrelated lists was randomized and fixed across participants. Each block consisted of either only related or only unrelated words. The visual fixation blocks consisted of crosshair fixation. Finally, a brief instruction (”Learn the following pairs of words”) was presented to the subjects prior to each block. During practice one week prior to scanning, participants were told to combine the two words in their memory and that their memory would be tested later.

Recognition accuracy was tested by asking participants to perform a recognition judgment task on 16 lists of eight word-pairs: four pairs that had been presented previously (target) and four pairs composed either of one word presented previously and one new word or of two words that belonged to different pairs (foils). A brief instruction (”Determine if the two words were presented together during the study phase”) was presented to the subjects prior to each block. Emphasis was placed on the fact that a positive answer should be provided when the two words had been seen as a pair. All lists were equivalent in terms of words frequency and semantic relatedness. The fMRI data from the retrieval phase are presented in a separate paper and will not be discussed further here.

Data acquisition

Magnetic Resonance Imaging (MRI) was performed using a SIEMENS 3T Magnetom TRIO a TIM System (Erlangen, Germany) at the Unité de Neuroimagerie Fonctionnelle (UNF) of the Institut Universitaire de Gériatrie de Montréal. Functional MR images were acquired using Gradient-Echo Echo-Planar imaging sequences (GE-

EPI) sensitive to blood oxygen level-dependent (BOLD) contrast (TR/TE = 2000/30 ms, flip angle = 90 deg; 31 interleaved slices, voxel size = 3.75 mm x 3.75 mm x 5 mm with a gap of 1 mm, field of view = 240 mm, matrix = 64*64). A 3-D structural image was taken at the end of the session and consisted of a sagittal T1-weighted 3D-MPRAGE sequence (TR/TE = 1950/3.93 ms, flip angle = 15 deg; 176 slices, voxel size = 1 mm x 1 mm x 1 mm, field of view = 256 mm, matrix = 256*256).

Image processing and data analysis

Data were analyzed in MATLAB 7.0 (http://www.mathworks.com) using the statistical parametric mapping software SPM5 (http://www.fil.ion.ucl.ac.uk/spm/). Functional images were first converted into Analyze format and unwarped. They were then realigned to the first acquired volume in the session, and a mean realigned volume was created for each subject. All the realigned volumes for each subject were spatially normalized into the Montreal Neurological Institute stereotactic space and spatially smoothed with an 8-mm Gaussian kernel. Low-frequency noise was removed with a high-pass filter of 208 sec. The instruction blocks were modeled as a condition of no-interest. A single-subject analysis was carried out in order to evaluate the individual contrasts (encoding semantically related vs visual fixation & encoding unrelated vs visual fixation) for each subject. A Random Effects (RFX) analysis was then performed on the contrast images by calculating a two-way ANOVA with Groups (healthy older adults, MCI higher-cognition, MCI lower-cognition) as a between-subjects factor, and Conditions (encoding semantically related, encoding unrelated) as a within-subjects factor, with non-sphericity correction, replications over subjects, and with correlated repeated measures. A conjunction analysis was performed to highlight the common

regions of activation in all three groups. A threshold of $p < 0.05$ family-wise corrected (FWE) with 10 contiguous voxels was used for the within-group analyses. For the between-group analyses, a more liberal threshold of $p < 0.001$ (uncorrected, with 5 continguous voxels) was used in accordance with what has been used most frequently in the MCI fMRI literature (10, 34-37). In addition, the p-values associated with a cluster-level correction were also calculated. As mentioned in the results section, all neuroimaging analyses were performed with the performance scores (percentage of correctly recognized pairs) of each subject as a covariate.

In a second step, two ROI images of the hippocampus bilaterally were created with WFU Pickatlas (38) and the between-group analyses were performed again on this ROI with a less stringent threshold ($p<0.005$ uncorrected, with 5 continguous voxels). Then, the average beta values of the hippocampal voxels that showed group differences were extracted with marsbar (39) for each group and they were correlated to the MDRS score of the MCI participants.

Results

Sociodemographic and neuropsychological data

Clinical data is shown in Table 1. One-way ANOVAs with Group (healthy controls, MCI higher-cognition, and MCI lower-cognition) as a between-subject factor indicated no age, $F(2,37) = 0.15$, N.S., or education, $F(2,37) = 0.64$, N.S., differences. Chi square analyses indicated a similar male to female ratio in the three groups ($\chi^2 = 0.05$, $\chi^2 = 0.03$, $\chi^2 = 0.16$, healthy controls vs MCI higher-cognition, healthy controls vs

MCI lower-cognition, and MCI higher-cognition vs MCI lower-cognition respectively, all N.S.)

One-way ANOVAs with Group (healthy controls, MCI higher-cognition, and MCI lower-cognition) as a between-subjects factor were also computed on cognitive measures (Supplement 1). Unsurprisingly, both MCI subgroups showed lower episodic memory capacities than healthy controls, but there was a greater impairment observed in the MCI lower-cognition than MCI higher-cognition subgroup (based on Tukey's post hoc). As expected, the MCI lower-cognition group showed a MDRS score significantly lower than that of healthy controls.

The group of MCI higher-cognition was composed of 5 amnestic single-domain MCI and 8 amnestic multiple-domain MCI whereas the MCI lower-cognition group was composed of 4 amnestic single-domain MCI and 9 amnestic multiple-domain MCI. This difference was not significant ($\chi^2 = 0.17$, N.S.).

Behavioral data

The mean percentage of correctly recognized pairs in the fMRI task is illustrated in Figure 1 for both conditions and for the three groups. A two–way ANOVA using Group (healthy controls, MCI higher-cognition, and MCI lower-cognition) as a between-subject factor and Condition (semantically related, unrelated) as a within-subject factor was computed on the mean percentage of correctly recognized pairs. A significant Group effect was observed, $F(2,37) = 9.87$, $p < 0.001$, but no Condition effect or Group by Condition interaction could be found. Tukey's post-hoc test revealed that both healthy controls and MCI higher-cognition performed significantly better than MCI lower-

cognition, $p < 0.001$ for both groups, and that the performances of the healthy controls and of the MCI higher-cognition groups were not significantly different (See Supplement 1 for correlations with neuropsychological data). As a group difference on performance was observed, all neuroimaging analyses used performance scores as a covariate.

Functional measures

Within-group comparisons

See Supplement 1 for Main Group effect and interaction.

Semantically related condition. Table 2 shows group activation results for the encoding semantically related contrast (Encoding > Visual fixation). The conjunction analysis showed that all three groups activated the occipital lobe bilaterally, the left inferior and superior parietal lobules and precuneus, and the left prefrontal cortex (Figure 2a). In addition, the healthy controls and the MCI higher-cognition groups activated the medial prefrontal cortex and anterior cingulate cortex bilaterally. The MCI higher-cognition group additionally activated the right prefrontal cortex and the right inferior and superior parietal lobules and precuneus. The activation of the left prefrontal cortex in healthy controls and in MCI lower-cognition groups, as opposed to the bilateral activation of the prefrontal cortex in MCI higher-cognition group, is illustrated in Figure 3 (a, b, c).

Semantically unrelated condition. Table 3 shows group activation results for encoding unrelated contrast (Encoding > Visual fixation). The conjunction analysis showed that the three groups activated the occipital lobe bilaterally, the left inferior and superior parietal lobules and precuneus, and the left prefrontal cortex (Figure 2b). In

addition, the healthy controls and the MCI higher-cognition groups activated the medial prefrontal cortex and anterior cingulate cortex bilaterally. The MCI higher-cognition group additionally activated the right prefrontal cortex, the superior parietal lobule and precuneus and the right cerebellum. Also, the MCI higher-cognition and the MCI lower-cognition groups showed additional activations in the right inferior parietal lobule. Figure 3 (d, e, f) illustrates the activation of the left prefrontal cortex in healthy controls and in MCI lower-cognition groups as opposed to the bilateral activation of the prefrontal cortex in MCI higher-cognition group.

Comparison of MCI subgroups and healthy controls

Table 4 shows areas of activation that differ significantly between MCI subgroups and healthy controls. When encoding semantically related word pairs, MCI higher-cognition showed significantly more activation than healthy controls in the right dorsolateral prefrontal cortex, in the right ventrolateral prefrontal cortex, and in the right premotor and motor areas. In contrast, MCI lower-cognition showed less activation than healthy controls in the right occipital lobe and the left inferior parietal lobule, while showing more activation in a more dorsal cluster within the left inferior parietal lobule. Comparison of the two MCI groups indicated that MCI higher-cognition showed more activation than MCI lower-cognition in the left temporal region, in the right precentral gyrus, in the right dorsolateral prefrontal cortex, in the right superior parietal lobule, and in the left inferior and superior parietal lobules. No regions were significantly more activated in MCI lower-cognition than in MCI higher-cognition. When encoding unrelated word pairs, MCI higher-cognition showed more activation than healthy controls in the right dorsolateral prefrontal cortex. Comparison of the two MCI groups

indicated that MCI higher-cognition showed more activation than MCI lower-cognition in the left parahippocampal gyrus and in the left superior parietal lobule. Again, no regions were significantly more activated in MCI lower-cognition than in MCI higher-cognition.

The ROI analyses indicated that MCI higher-cognition showed significantly more activation than healthy controls in the left hippocampus during the unrelated condition (Figure 3). Pearson correlations were calculated between the beta values of all MCI individuals and their MDRS scores. A positive correlation was found ($r = 0.48$, $p = 0.01$), indicating a lower activation of the left hippocampus in MCI persons with lower MDRS scores (Figure 4).

Discussion

Healthy older adults activated a memory network that includes the left superior and inferior parietal lobe, the left precuneus, the left lateral prefrontal cortex, the occipital lobe bilaterally, the medial prefrontal cortex bilaterally and the anterior cingulate gyrus bilaterally. The encoding of semantically related word pairs activated additional regions of the ventrolateral prefrontal cortex (BA 45). BA 45 has been involved in semantic processing and elaboration (40, 41) and in semantic memory encoding of semantically related word pairs (42).

The two MCI subgroups activated a relatively similar network but interesting differences were observed. As a preamble, it is of note that MCI higher-cognition performed the fMRI task similarly to the healthy controls even though they showed

objective memory deficits during the neuropsychological evaluation. This might be due to the fact that recognition was used in the fMRI, a condition that is less sensitive to the MCI-related memory impairment (43) and more amenable to compensation effects in MCI persons. This is supported by the pattern of brain activation found among MCI with higher cognition: they showed significantly more activation than healthy controls in a number of areas of the right prefrontal cortex (BA 4-6-8-9-45-46) during the two encoding conditions and in the left hippocampus during the encoding of unrelated word pairs. Increase in brain activation has been typically reported as reflecting either 1) compensatory mechanisms that would work against lesion-related deficits in brain function and that would improve performance, (6, 44-46) or 2) dedifferentiation or nonselective recruitment, which would reflect a generalized non-functional spread of activity that is not relevant to the task (47, 48). The fact that the MCI higher-cognition subjects in this study obtained performances comparable to those of healthy controls suggests that their additional right prefrontal and left hippocampus activations reflect compensatory mechanisms. It is interesting to note that most of the additional activations of the MCI higher-cognition were found in areas controlateral to the regions activated in healthy controls, a pattern that has been also found in compensating healthy older adults (see HAROLD model, 49, and 50). Alternatively, the recruitment of the contralateral hemisphere could reflect the activation of a degenerated system that is structurally different from the one activated in healthy controls but that can serve the same function (3, 4, 51).

By contrast, MCI lower-cognition were significantly less accurate on the verbal learning fMRI task and failed to show increased prefrontal and hippocampal activation,

suggesting an inability to compensate for their deficits. Furthermore, they showed less activation than controls (hypoactivation) in posterior regions on both sides. It is noteworthy that the fMRI effects with MCI lower-cognition would be augmented if the results were not covaried for performance. However, this covariation was necessary in order to reduce a confounding effect between disease severity and activations. The increase of hippocampal activation in MCI higher-cognition, but not in MCI lower-cognition, is similar to what has been observed by Celone and colleagues (8) who found that the less impaired older patients had more activation in their hippocampi whereas more impaired patients had less activations in their hippocampi. Interestingly, many memory encoding studies have found hypoactivations in AD (8, 52-55), suggesting that MCI persons with more severe cognitive deficits show a functional brain activation pattern similar to the one observed in AD. Our results and those of Celone et al, contrast with the findings reported by Miller and colleagues (56) who reported larger hippocampal activation in MCI with a more rapid decline. These divergent results might be due to their use of an easier task and/or inclusion of slightly milder patients.

The compensation breakdown during the MCI stage is also supported by our finding of a positive correlation between the left hippocampus activation and the MDRS score of MCI individuals, which suggests reduced activation of this structure as the disease progresses. Importantly, most of the group differences in activation were located in frontal and parietal regions, areas that have been shown to accumulate an increased level of amyloid deposition, as measured with PET imaging of Pittsburgh's Compound-B, in Alzheimer's disease patients (57-61). The finding of brain activation in AD-related

brain areas is crucial as the model predicts that these functional changes should happen in regions that suffer from neural damage.

There are a few limitations that must be discussed. First, our use of a clinical measure as an indicator of disease severity may not be ideal. However, because there is no gold standard for severity measure, we favoured a measure of global cognitive performance as it is closer to the current criteria for identifying MCI and AD than are neuroanatomical markers. Moreover, one may criticize our use of a median-split rather than regressions strategy. However, we predicted that brain activation would follow a nonlinear trajectory, a pattern that is not easily amenable to regression analyses. Another limitation is our use of a low-level control task rather than a high-level control task such as passive reading. However, this could have overshadowed the interpretation of the results, as it has been shown that MCI persons and healthy controls show different brain activation patterns during word reading (62). Finally, our use of a blocked design does not allow a comparison of correct and incorrect responses. However, blocked designs offer maximal detection power (63), which is crucial to highlight differences related to severity levels.

To conclude, our study indicates a progression within the MCI phase. Compensation and hyperactivation of the right prefrontal cortex and of the left hippocampus characterize MCIs with less severe cognitive deficits, while breakdown of compensation and hypoactivation of the posterior regions characterize MCIs with more severe cognitive deficits. Our fMRI analyses were covaried for performance level and it is therefore unlikely that the different brain activation patterns are solely explained by

differences in motivation or in attention. Our results suggest that divergent fMRI results in the MCI literature might be explained by different levels of severity among the MCI patients from the different studies and hence by different compensation capacities. Those findings could have tremendous implications for therapeutic efforts because they suggest that persons with MCI retain the capacity to develop neural compensation. In addition, they have implications for those wishing to use fMRI as a brain surrogate to assess the effects of treatment. First, our results allows predictions regarding how treatments promoting cognitive or brain compensations should modulate brain activation in MCI. In addition, they offer a measure of treatment outcome by connecting the cerebral activation pattern to the cognitive impairment severity.

Acknowledgement

This work was supported by a grant from Canadian Institutes of Health Research (CIHR) to SB. SB received a National Research Award from the Fonds de la Recherche en Sante du Quebec (FRSQ) and FC was supported by a doctoral scholarship from CIHR. We thank Émilie Lepage, Fanny-Maude Urfer, and Rosalie Perron for the neuropsychological evaluation of the participants, the clinical neuropsychology service of the IUGM (Chief, Francine Fontaine, Ph.D) for their contribution to the interpretation of test results, Dr Serge Gauthier, Dr Christian Bocti and the IUGM cognition clinic (Director: Dr Marie-Jeanne Kergoat) for MCI referral, Samira Mellah for assistance in task construction and data collection, and Ellen Mosco for editorial assistance. The authors have reported no conflicts of interest.

Financial Disclosures

The authors do not report any conflict of interest.

References

1. Schroder J, Buchsbaum MS, Shihabuddin L, Tang C, Wei TC, Spiegel-Cohen J, et al. (2001): Patterns of cortical activity and memory performance in Alzheimer's disease. *Biol Psychiatry*. 49:426-436.

2. Bennett DA, Wilson RS, Schneider JA, Evans DA, Beckett LA, Aggarwal NT, et al. (2002): Natural history of mild cognitive impairment in older persons. *Neurology*. 59:198-205.

3. Friston KJ, Price CJ (2003): Degeneracy and redundancy in cognitive anatomy. *Trends Cogn Sci*. 7:151-152.

4. Price CJ, Friston KJ (2002): Degeneracy and cognitive anatomy. *Trends Cogn Sci*. 6:416-421.

5. Prvulovic D, Van de Ven V, Sack AT, Maurer K, Linden DE (2005): Functional activation imaging in aging and dementia. *Psychiatry Res*. 140:97-113.

6. Scarmeas N, Zarahn E, Anderson KE, Hilton J, Flynn J, Van Heertum RL, et al. (2003): Cognitive reserve modulates functional brain responses during memory tasks: a PET study in healthy young and elderly subjects. *Neuroimage*. 19:1215-1227.

7. Dickerson BC, Sperling RA (2008): Functional abnormalities of the medial temporal lobe memory system in mild cognitive impairment and Alzheimer's disease: insights from functional MRI studies. *Neuropsychologia*. 46:1624-1635.

8. Celone KA, Calhoun VD, Dickerson BC, Atri A, Chua EF, Miller SL, et al. (2006): Alterations in memory networks in mild cognitive impairment and Alzheimer's disease: an independent component analysis. *J Neurosci*. 26:10222-10231.

9. Johnson SC, Schmitz TW, Moritz CH, Meyerand ME, Rowley HA, Alexander AL, et al. (2006): Activation of brain regions vulnerable to Alzheimer's disease: The effect of mild cognitive impairment. *Neurobiol Aging*. 27:1604-1612.

10. Machulda MM, Ward HA, Borowski B, Gunter JL, Cha RH, O'Brien PC, et al. (2003): Comparison of memory fMRI response among normal, MCI, and Alzheimer's patients. *Neurology*. 61:500-506.

11. Kircher T, Weis S, Freymann K, Erb M, Jessen F, Grodd W, et al. (2007): Hippocampal activation in MCI patients is necessary for successful memory encoding. *J Neurol Neurosurg Psychiatry*. 78:812-818.

12. Dickerson BC, Salat DH, Greve DN, Chua EF, Rand-Giovannetti E, Rentz DM, et al. (2005): Increased hippocampal activation in mild cognitive impairment compared to normal aging and AD. *Neurology*. 65:404-411.

13. Hamalainen A, Pihlajamaki M, Tanila H, Hanninen T, Niskanen E, Tervo S, et al. (2007): Increased fMRI responses during encoding in mild cognitive impairment. *Neurobiol Aging*. 28:1889-1903.

14. Dannhauser TM, Shergill SS, Stevens T, Lee L, Seal M, Walker RW, et al. (2008): An fMRI study of verbal episodic memory encoding in amnestic mild cognitive impairment. *Cortex*. 44:869-880.

15. Mandzia J, Black S, Grady C, McAndrews MP, Graham S (2002): Encoding and retrieval in aging and memory loss, a fMRI study. *Brain Cogn*. 49:225-228.

16. Mandzia JL, McAndrews MP, Grady CL, Graham SJ, Black SE (2007): Neural correlates of incidental memory in mild cognitive impairment: An fMRI study. *Neurobiol Aging*. doi:10.1016/j.neurobiolaging.2007.08.024.

17. Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV, et al. (2001): Current concepts in mild cognitive impairment. *Arch Neurol*. 58:1985-1992.

18. Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, et al. (2004): Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *J Intern Med*. 256:240-246.

19. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E (1999): Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol*. 56:303-308.

20. Desrosiers J, Bravo G, Hebert R, Dubuc N (1995): Reliability of the revised functional autonomy measurement system (SMAF) for epidemiological research. *Age Ageing*. 24:402-406.

21. Buschke H (1984): Cued recall in amnesia. *Journal of Clinical Neuropsychology*. 6:433-440.

22. Van der Linden M, Adam S, Agniel A, Baisset-Mouly C, Bardet F, Coyette F, et al. (2004): *L'évaluation de troubles de la mémoire: présentation de quatre tests de mémoire épisodique (avec étalonnage)*. Marseille: Solal.

23. Signoret JL (1991): *Batterie d'efficience mnésique BEM 144*. Paris: Elsevier.

24. Rey A (1959): *Test de copie d'une figure complexe: manuel*. Paris: Les éditions du centre de psychologie appliquée.

25. Regard M (1981): Cognitive rigidity and flexibility: a neuropsychological study. University of Victoria, Canada.

26. Benton AL, Hamsher K, Varney NR, Spreen O (1983): *Contributions to neuropsychological assessment*. New York: Oxford University Press.

27. Wechsler D (1997): *Wechsler Adult Intelligence Scale-III.* New York: Psychological Corporation.

28. Kaplan EF, Goodglass H, Weintraub S (1983): *The Boston Naming Test (2nd edition)*. Philadelphia, PA: Lea & Febiger.

29. Mattis S (1976): Mental status examination for organic mental syndrome in the elderly patient. In: Bellak L, Karasu TB, editors. *Geriatric Psychiatry*. New York: Grune & Stratton.

30. Folstein MF, Folstein SE, McHugh PR (1975): Mini-Mental State: A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*. 12:189-198.

31. Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, et al. (2005): The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 53:695-699.

32. Freibergs V (1968): *Normes d'association libre aux 100 mots Kent-Rosanoff* Université de Montréal. Institut de psychologie. ed.

33. Freibergs V (1970): *Normes d'association libre aux premières cinq réponses des hiérarchies d'associations aux 100 mots Kent-Rosanoff* Université de Montréal. Institut de psychologie. ed.

34. Sole-Padulles C, Bartres-Faz D, Junque C, Vendrell P, Rami L, Clemente IC, et al. (2007): Brain structure and function related to cognitive reserve variables in normal aging, mild cognitive impairment and Alzheimer's disease. *Neurobiol Aging (2007), doi:101016/jneurobiolaging200710008*.

35. Heun R, Freymann K, Erb M, Leube DT, Jessen F, Kircher TT, et al. (2007): Mild cognitive impairment (MCI) and actual retrieval performance affect cerebral activation in the elderly. *Neurobiol Aging*. 28:404-413.

36. Heun R, Freymann K, Erb M, Leube DT, Jessen F, Kircher TT, et al. (2006): Mild cognitive impairment (MCI) and actual retrieval performance affect cerebral activation in the elderly. *Neurobiol Aging*.

37. Ries ML, Schmitz TW, Kawahara TN, Torgerson BM, Trivedi MA, Johnson SC (2005): Task-dependent posterior cingulate activation in mild cognitive impairment. *Neuroimage*. 29:485-492.

38. Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH (2003): An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage*. 19:1233-1239.

39. Brett M, Anton J-L, Valabregue R, Poline J-P (2002): Region of interest analysis using an SPM toolbox *8th International Conference on Functional Mapping of the Human Brain, June 2-6, 2002,*. Sendai, Japan. Available on CD-ROM in NeuroImage, Vol 16, No 2.

40. Fletcher PC, Henson RN (2001): Frontal lobes and human memory: insights from functional neuroimaging. *Brain*. 124:849-881.

41. Poldrack RA, Wagner AD, Prull MW, Desmond JE, Glover GH, Gabrieli JD (1999): Functional specialization for semantic and phonological processing in the left inferior prefrontal cortex. *Neuroimage*. 10:15-35.

42. Kapur S, Tulving E, Cabeza R, McIntosh AR, Houle S, Craik FI (1996): The neural correlates of intentional learning of verbal materials: a PET study in humans. *Brain Res Cogn Brain Res*. 4:243-249.

43. Collie A, Maruff P, Currie J (2002): Behavioral characterization of mild cognitive impairment. *J Clin Exp Neuropsychol*. 24:720-733.

44. Grady CL, McIntosh AR, Beig S, Keightley ML, Burian H, Black SE (2003): Evidence from functional neuroimaging of a compensatory prefrontal network in Alzheimer's disease. *J Neurosci*. 23:986-993.

45. Cabeza R, Anderson ND, Locantore JK, McIntosh AR (2002): Aging gracefully: Compensatory brain activity in high-performing older adults. *Neuroimage*. 17:1394-1402.

46. Grady CL, McIntosh AR, Craik FI (2005): Task-related activity in prefrontal cortex and its relation to recognition memory performance in young and old adults. *Neuropsychologia*. 43:1466-1481.

47. Logan JM, Sanders AL, Snyder AZ, Morris JC, Buckner RL (2002): Under-recruitment and nonselective recruitment: dissociable neural mechanisms associated with aging. *Neuron*. 33:827-840.

48. Li S-C, Lindenberger U (1999): Cross-level unification: A computational exploration of the link between deterioration of neurotransmitter systems dedifferentiation of cognitive abilities in old age. In: L.-G. Nilsson and H. J. Markowitsch E, editor. *Cognitive Neuroscience of Memory*. Seattle: Hogrefe & Huber, pp 103–146.

49. Cabeza R (2002): Hemispheric asymmetry reduction in older adults: the HAROLD model. *Psychol Aging*. 17:85-100.

50. Banich MT (1998): The missing link: the role of interhemispheric interaction in attentional processing. *Brain Cogn*. 36:128-157.

51. Edelman GM, Gally JA (2001): Degeneracy and complexity in biological systems. *Proc Natl Acad Sci U S A*. 98:13763-13768.

52. Small SA, Perera GM, DeLaPaz R, Mayeux R, Stern Y (1999): Differential regional dysfunction of the hippocampal formation among elderly with memory decline and Alzheimer's disease. *Ann Neurol*. 45:466-472.

53. Rombouts SA, Barkhof F, Veltman DJ, Machielsen WC, Witter MP, Bierlaagh MA, et al. (2000): Functional MR imaging in Alzheimer's disease during memory encoding. *AJNR Am J Neuroradiol*. 21:1869-1875.

54. Golby A, Silverberg G, Race E, Gabrieli S, O'Shea J, Knierim K, et al. (2005): Memory encoding in Alzheimer's disease: an fMRI study of explicit and implicit memory. *Brain*. 128:773-787.

55. Kato T, Knopman D, Liu H (2001): Dissociation of regional activation in mild AD during visual encoding: a functional MRI study. *Neurology*. 57:812-816.

56. Miller SL, Fenstermacher E, Bates J, Blacker D, Sperling RA, Dickerson BC (2008): Hippocampal activation in adults with mild cognitive impairment predicts subsequent cognitive decline. *J Neurol Neurosurg Psychiatry*. 79:630-635.

57. Forsberg, A., Engler, H., Almkvist, O., Blomquist, G., Hagman, G., Wall, A., et al. (2008). PET imaging of amyloid deposition in patients with mild cognitive impairment. *Neurobiol Aging, 29*(10), 1456-1465.

58. Frisoni, G. B., Lorenzi, M., Caroli, A., Kemppainen, N., Nagren, K., & Rinne, J. O. (2009). In vivo mapping of amyloid toxicity in Alzheimer disease. *Neurology, 72*(17), 1504-1511.

59. Kemppainen, N. M., Aalto, S., Wilson, I. A., Nagren, K., Helin, S., Bruck, A., et al. (2007). PET amyloid ligand [11C]PIB uptake is increased in mild cognitive

impairment. *Neurology, 68*(19), 1603-1606.

60. Klunk, W. E., Engler, H., Nordberg, A., Wang, Y., Blomqvist, G., Holt, D. P., et al. (2004). Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Ann Neurol, 55*(3), 306-319.

61. Rowe, C. C., Ng, S., Ackermann, U., Gong, S. J., Pike, K., Savage, G., et al. (2007). Imaging beta-amyloid burden in aging and dementia. *Neurology, 68*(20), 1718-1725.

62. Vandenbulcke M, Peeters R, Dupont P, Van Hecke P, Vandenberghe R (2007): Word reading and posterior temporal dysfunction in amnestic mild cognitive impairment. *Cereb Cortex*. 17:542-551.

63. Liu TT (2004): Efficiency, power, and entropy in event-related fMRI with multiple trial types. Part II: design of experiments. *Neuroimage*. 21:401-413.

Table 1.

Demographic variables and scores on the neuropsychological tasks for the three groups.

	Controls n = 14	MCI higher-cognition n = 13	MCI lower-cognition n = 13
Gender	8F/6M	8F/5M	7F/6M
Age	67.21 (6.80)	68.62 (10.30)	67.08 (6.29)
Education	14.57 (3.76)	15.31 (3.83)	13.62 (3.91)
MDRS	140.33 (2.65)	139.31 (2.81)	129.92 (4.48)[b]
MMSE	29.29 (1.14)	28.85 (1.57)	26.46 (1.56)[b]
MOCA	27.64 (1.39)		
SMAF		-0.83 (0.83)	-1.33 (1.13)
Modified Boston Naming Test (/15)		13.92 (1.12)	12.46 (1.71)[c]
Coding (WAIS-III)	11.29 (2.30)	9.77 (2.65)	8.92 (2.69)
Benton Judgment of line orientation		24.85 (3.58)	22.62 (4.11)
Copy of Rey's Figure (time)		216.69 (105.64)	251.38 (144.08)
Copy of Rey's Figure (score)		31.35 (3.26)	30.08 (3.48)
Immediate recall of Rey's Figure (score)		12.46 (5.19)	8.27 (5.99)
Delayed recall of Rey's Figure (score)		13.81 (4.99)	7.34 (5.21)[d]
Stroop 3rd plate (time)		29.68 (6.78)	32.57 (8.56)
Stroop 3rd plate (errors)		0.92 (1.04)	1.54 (2.54)
RL/RI-16 3rd free recall	12.21 (2.32)	10.15 (2.54)	5.23 (2.59)[b,e]
RL/RI-16 delayed free recall	12.71 (2.40)	9.52 (3.86)[a]	4.85(3.08)[b,e]

Note. [a] impairment relative to the controls at $p < 0.05$; [b] impairment relative to the controls at $p < 0.001$; [c] impairment relative to the MCI higher-cognition at $p < 0.05$; [d] impairment relative to the MCI higher-cognition at $p < 0.01$; [e] impairment relative to the MCI higher-cognition at $p < 0.001$

Table 2

Clusters (>10 voxels) significantly more activated during the encoding of semantically related word pairs condition than during the visual fixation condition for healthy controls, MCI higher-cognition, and MCI lower-cognitions with cluster size, peak voxel MNI coordinates and corresponding t-values.

Activates areas (Brodmann area) ($p < 0.05$, corrected)	Cluster Size	x	y	z	t value
Healthy controls: Encoding semantically related > visual fixation					
Left occipital lobe (17, 18, 19)	286 (20020 µl)	-15	-90	-6	8.56
Right occipital lobe (17, 18)	126 (8820 µl)	18	-87	-3	8.34
Left inferior/ superior parietal lob. and precuneus (7, 39, 40)	49 (3430 µl)	-30	-69	36	6.63
Left prefrontal cortex (9, 44, 45, 46)	42 (2940 µl)	-45	15	30	6.39
Left prefrontal cortex (6, 9)	18 (1260 µl)	-45	0	39	5.99
Left/Right medial prefrontal cortex & anterior cingulate cortex (6, 8, 24, 32)	35 (2450 µl)	6	12	48	5.98
MCI higher-cognition: Encoding semantically related > visual fixation					
Left occipital lobe (17, 18, 19)	318 (22260 µl)	-15	-90	-9	10.12
Right occipital lobe (17, 18)	190 (13300 µl)	18	-90	-3	8.22
Right inferior/superior parietal lob. and precuneus (7, 39)	46 (3220 µl)	33	-63	51	7.30
Right prefrontal cortex (6, 9, 44, 45)	57 (3990 µl)	42	0	42	7.08
Left prefrontal cortex (6, 9, 44, 45)	71 (4970 µl)	-39	0	36	6.50
Left inferior/superior parietal lob. and precuneus (7, 39, 40)	125 (8750 µl)	-30	-69	42	6.27

Right prefrontal cortex (46)	24 (1680 µl)	45	27	24	6.14
Left/Right medial prefrontal cortex and anterior cingulate cortex (8, 24, 32)	33 (2310 µl)	-6	6	51	5.93
MCI lower-cognition: Encoding semantically related > visual fixation					
Left occipital lobe (17, 18, 19)	290 (20300 µl)	-18	-90	-9	11.19
Right occipital lobe (17, 18)	133 (9310 µl)	27	-87	0	8.24
Left prefrontal cortex (6, 9, 44, 46)	146 (10220 µl)	-45	0	39	6.90
Left inferior parietal lobule (39)	22 (1540 µl)	-30	-69	39	6.10

Table 3

Clusters (>10 voxels) significantly more activated during the encoding of unrelated word pairs condition than during the visual fixation condition for healthy controls, MCI higher-cognition, and MCI lower-cognition with cluster size, peak voxel MNI coordinates and corresponding t-values.

Activates areas (Brodmann area) ($p < 0.05$, corrected)	Cluster Size	x	y	z	t value
Healthy controls: Encoding unrelated > visual fixation					
Left occipital lobe (17, 18, 19)	190 (13300 µl)	-39	-69	-12	7.26
Right occipital lobe (17, 18)	74 (5180 µl)	18	-87	-3	7.02
Left inferior/superior parietal lob. and precuneus (7, 39, 40)	47 (3290 µl)	-27	-72	36	6.37
Left prefrontal cortex (9, 44, 46)	42 (2940 µl)	-45	12	30	6.06
Left/Right medial prefrontal cortex and anterior cingulate cortex (6, 8, 32)	42 (2940 µl)	-6	3	54	5.74
Left prefrontal cortex (6)	12 (840 µl)	-45	0	39	5.70
MCI higher-cognition: Encoding unrelated > visual fixation					
Left occipitotemporal areas (17, 18, 19, 37)	403 (28210 µl)	-15	-90	-9	9.77
Right occipital lobe (17, 18)	170 (11900 µl)	18	-90	-3	8.42
Left prefrontal cortex (6, 9, 44)	181 (12670 µl)	-39	0	36	7.58
Right inferior/superior parietal lob. and precuneus (7, 39)	64 (4480 µl)	30	-63	48	7.12
Right prefrontal cortex (46)	20 (1400 µl)	45	27	24	6.28
Left superior parietal lobule	93 (6510 µl)	-30	-54	39	7.12

and precuneus (7)					
Left/Right medial prefrontal cortex	49 (3430 µl)	-6	6	51	6.06
and anterior cingulate cortex (6, 8, 32)					
Right prefrontal cortex (6, 9, 44)	27 (1890 µl)	42	3	39	5.87
Left inferior prefrontal cortex (46)	15 (1050 µl)	-42	30	21	5.85
Left inferior parietal lobule (40)	10 (700 µl)	-42	-45	42	5.42
Right cerebellum	33 (2310 µl)	36	-57	-21	5.40
MCI lower-cognition: Encoding unrelated > visual fixation					
Left occipital lobe (17, 18, 19)	188 (13160 µl)	-18	-90	-9	9.60
Right occipital lobe (17, 18)	98 (6860 µl)	27	-87	0	7.96
Left prefrontal cortex	227 (15890 µl)	-45	3	36	7.70
(6, 9, 44, 45, 46)					
Left inferior parietal lobule (40)	35 (2450 µl)	-27	-63	39	5.68
Right inferior parietal lobule (39)	11 (770 µl)	33	-63	36	5.66

Table 4.

Clusters (>5 voxels) significantly more activated in healthy controls than in MCI higher- and lower-cognition or significantly more activated in MCI higher and lover-cognition than in healthy controls, with cluster size, peak voxel MNI coordinates and corresponding t-values.

Activates areas (Brodmann area) ($p < 0.001$, uncorrected)	Cluster Size	x	y	z	t value
MCI higher-cognition > Healthy controls Encoding semantically related					
Right prefrontal cortex (4, 6, 9)	35 (2450 µl)	42	0	42	4.30
Right prefrontal cortex (45, 46)	25 (1750 µl)	48	27	21	4.17
MCI higher-cognition > Healthy controls Encoding unrelated					
Right prefrontal cortex (8, 9)	12 (840 µl)	46	6	39	3.78
Right prefrontal cortex (46)	5 (350 µl)	48	24	21	3.46
Left hippocampus	5 (350 µl)	-18	-33	-3	2.78*
MCI higher-cognition > MCI lower-cognition Encoding semantically related					
Left transverse temporal gyrus (13, 41, 43)	25 (1750 µl)	-51	-18	15	4.33
Right superior parietal lobule (7)	8 (560 µl)	33	-60	51	4.21
Left inferior parietal lobule (40)	10 (700 µl)	-30	-51	57	3.87
Right precentral gyrus (6)	20 (1400 µl)	42	-3	45	3.84
Left superior parietal lobule (7)	6 (42 µl)	-24	-66	54	3.64
Right middle frontal gyrus (9)	6 (42 µl)	27	27	36	3.52
MCI higher-cognition > MCI lower-cognition Encoding unrelated					
Left parahippocampal gyrus	8 (56 µl)	-21	-42	-15	3.72
Left superior parietal lobule (7)	8 (56 µl)	-15	-72	54	3.62

Healthy controls > MCI lower-cognition Encoding semantically related					
Right occipital lobe (18)	17 (1190 µl)	21	-81	12	3.75
Left inferior parietal lobule (40)	14 (980 µl)	-30	-51	57	3.65
MCI lower-cognition> Healthy controls Encoding semantically related					
Left inferior parietal lobule (40)	6 (420 µl)	-54	-57	39	3.80

*p < 0.005 (ROI analysis)

Figure Caption

Figure 1. Scores obtained on the encoding of semantically related word pairs condition and on the encoding of unrelated word pairs condition by the Healthy controls, MCI higher-cognition, and MCI lower-cognition groups. Note. * $p < 0.05$.

Figure 2. Conjunction analysis and cerebral activations ($p < 0.05$, corrected, cluster size > 5) of healthy controls, MCI higher-cognition, and MCI lower-cognition during encoding of semantically related word pairs and during encoding of unrelated word pairs for healthy controls (a and b, respectively).

Figure 3. Cerebral activations ($p < 0.05$, corrected, cluster size > 5) during encoding of semantically related word pairs and during encoding of unrelated word pairs for healthy controls (a and d, respectively), MCI higher-cognition (b and e, respectively), and MCI lower-cognition (c and f, respectively). The Z-coordinate is 110 for all slices.

Figure 4. Increased activation (*MCI higher-cognition > Healthy controls*, $p < 0.005$ uncorrected, cluster size > 5) in the MCI higher-cognition than in healthy controls during encoding of unrelated word pairs. The Y-coordinate is -34.

Figure 5. Scatter plot with fit line showing the significant correlations in MCI individuals between the scores on the MDRS and their beta values in the left hippocampus during the unrelated encoding condition. The dash line represents the mean beta values of the healthy controls.

Figure 1. Scores obtained on the encoding of semantically related word pairs condition and on the encoding of unrelated word pairs condition by the Healthy controls, MCI higher-cognition, and MCI lower-cognition groups. Note. * $p < 0.05$.

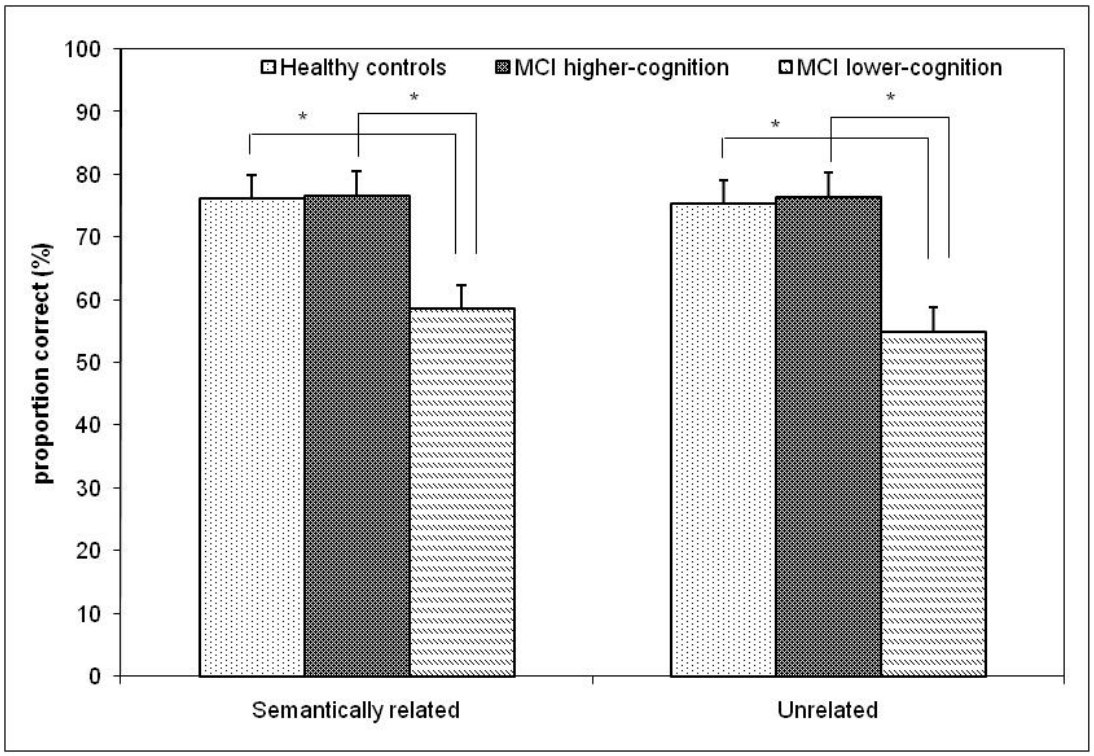


Figure 2. Conjunction analysis and cerebral activations ($p < 0.05$, corrected, cluster size > 5) of healthy controls, MCI higher-cognition, and MCI lower-cognition during encoding of semantically related word pairs and during encoding of unrelated word pairs for healthy controls (a and b, respectively).

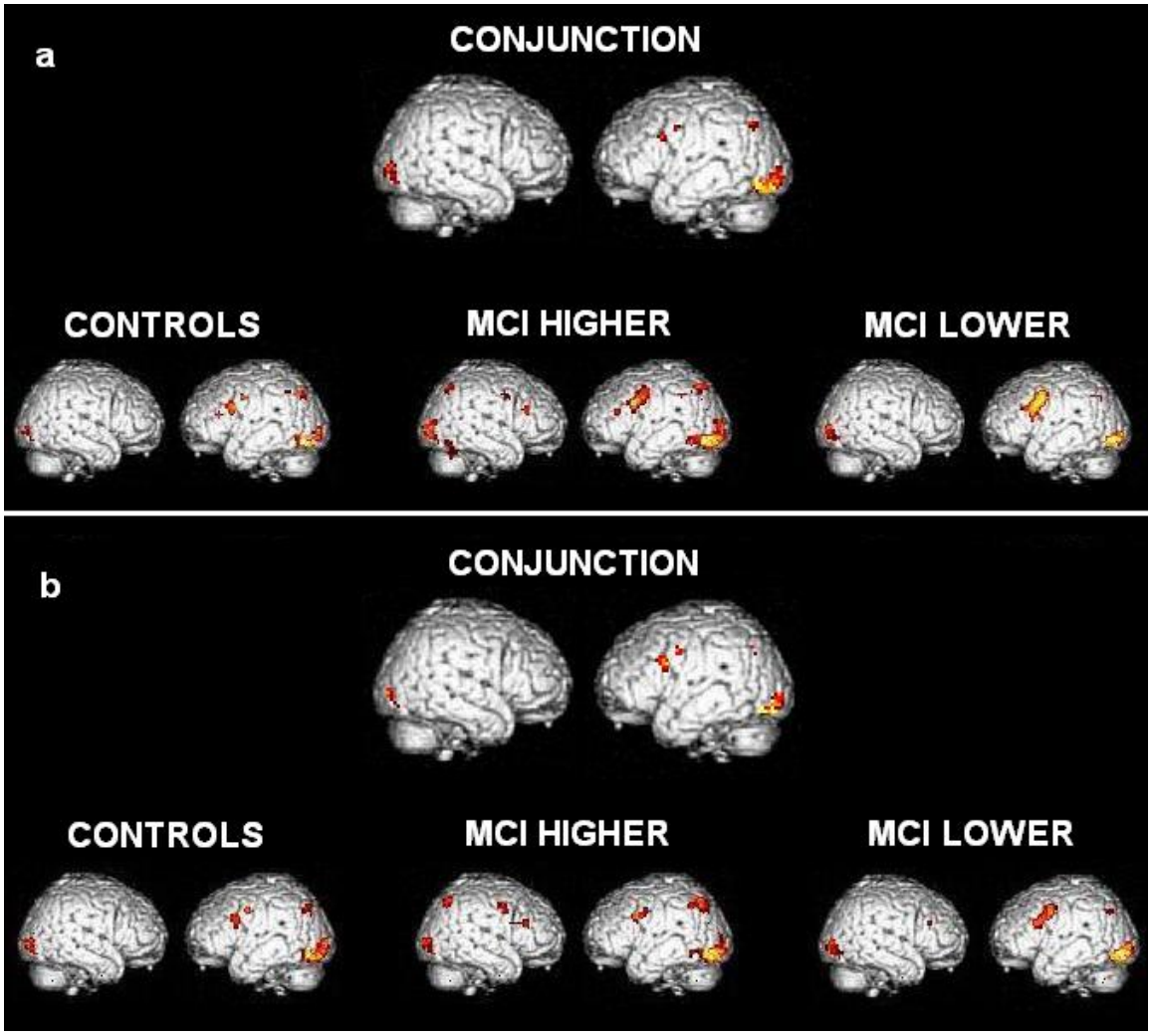


Figure 3. Cerebral activations ($p < 0.05$, corrected, cluster size > 5) during encoding of semantically related word pairs and during encoding of unrelated word pairs for healthy controls (a and d, respectively), MCI higher-cognition (b and e, respectively), and MCI lower-cognition (c and f, respectively). The Z-coordinate is 110 for all slices.

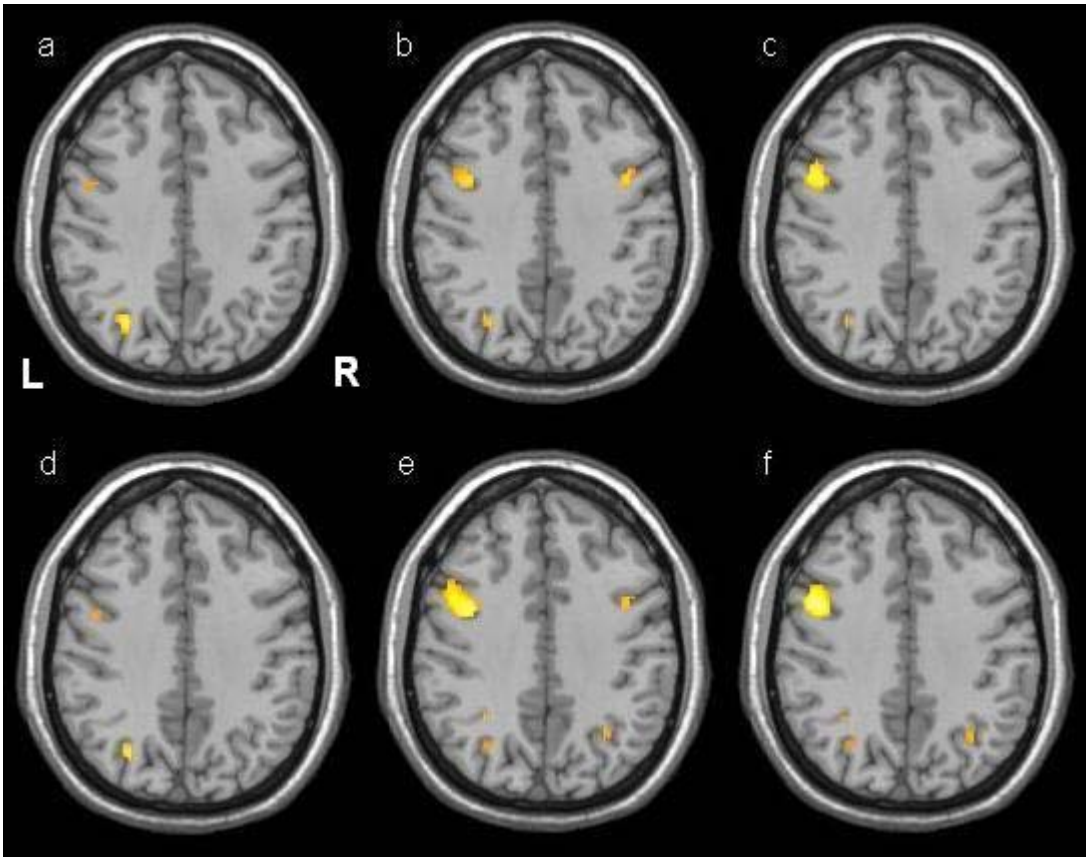


Figure 4. Increased activation (*MCI higher-cognition* > *Healthy controls*, $p < 0.005$ uncorrected, cluster size > 5) in the MCI higher-cognition than in healthy controls during encoding of unrelated word pairs. The Y-coordinate is -34.

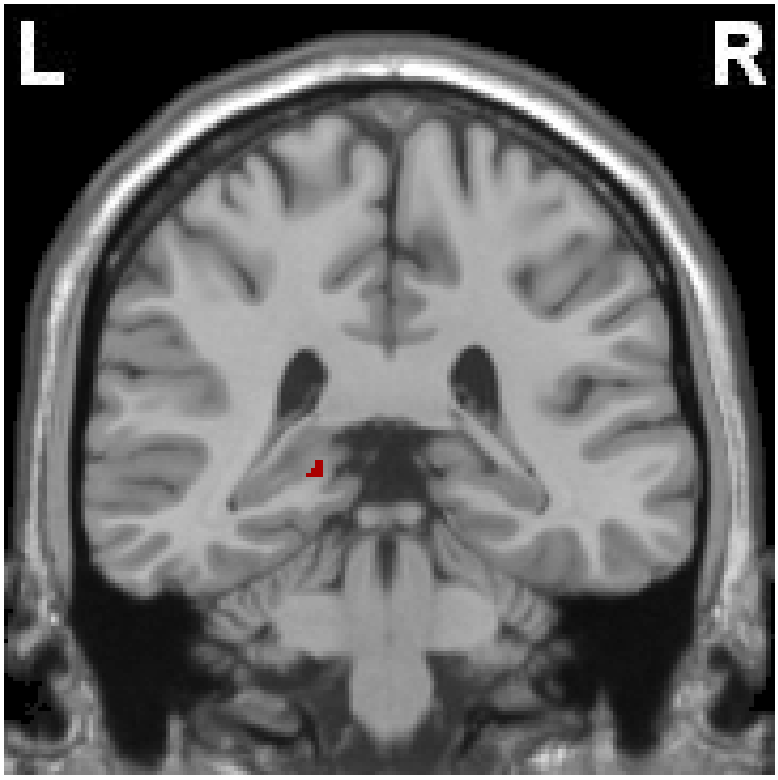
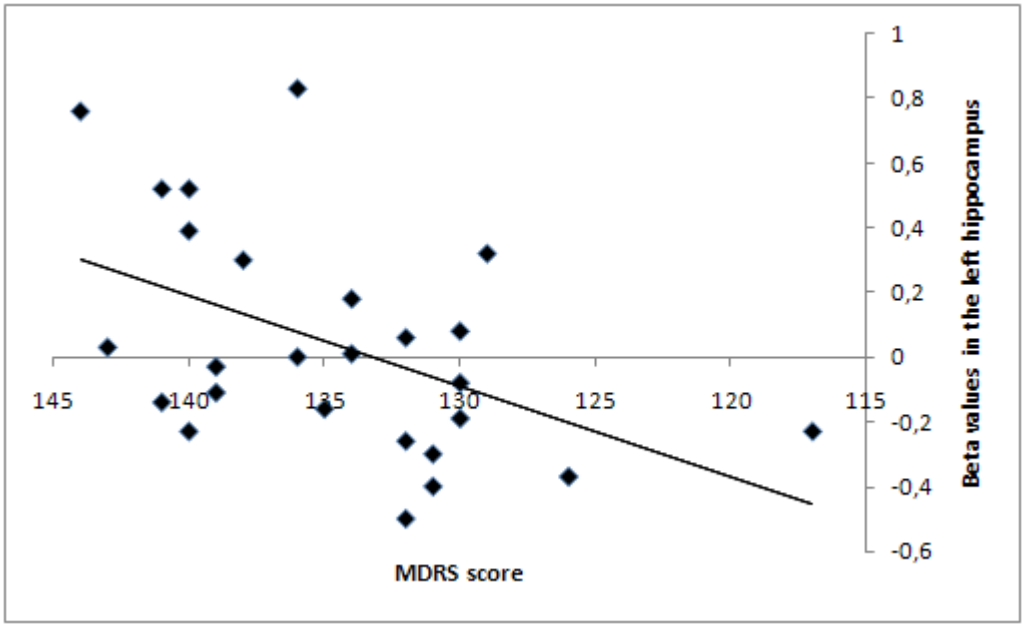


Figure 5. Scatter plot with fit line showing the significant correlations in MCI individuals between the scores on the MDRS and their beta values in the left hippocampus during the unrelated encoding condition. The dash line represents the mean beta values of the healthy controls.



CHAPITRE 5

Article n° 4

Effect of disease severity on neural compensation of item and associative recognition in mild cognitive impairment

Francis Clément & Sylvie Belleville

Journal of Alzheimer's Disease (sous presse)

Abstract

It is proposed that the prodromal phase of Alzheimer's disease is associated with additional brain activation in key regions involved in memory, reflecting compensatory brain plasticity. Very little is however known about the evolution of these compensatory mechanisms as the brain acquires more damages. We conducted an fMRI memory study measuring brain activation related to old/new (item recognition) and intact/rearranged (associative recognition) word-pair recognition paradigms in 26 persons with mild cognitive impairment (MCI) and 14 healthy older adults. The Mattis Dementia Rating Scale was used to divide persons with MCI into those with higher and lower cognitive performances. Results indicated more brain activation in MCIs than in controls but disease severity determined which cognitive process was associated with larger activation: Persons with less severe MCI showed hyperactivation during associative recognition only, whereas persons with more severe MCI showed hyperactivation during item recognition only. These hyperactivations were found mainly in brain areas that are typically associated with memory retrieval (e.g., bilateral prefrontal cortex and left inferior parietal lobule). These findings indicate that neural plasticity occurs during the entire MCI phase but that it is associated with different cognitive components: As they progress in the disease, individuals with MCI will experience a breakdown in the compensatory mechanisms for associative recognition accompanied by emergence of compensatory mechanisms for item recognition.

Keywords: Alzheimer's disease, episodic memory, cognition, magnetic resonance imaging

An important feature of Alzheimer's disease (AD) is that the associated brain lesions and the resulting cognitive deficits are progressive [1]. Yet and surprisingly, little is known regarding the evolution of the functional brain response to these growing damages. Most studies assumed that their MCI participants were equivalent in terms of disease severity and treated them as a single homogeneous group on this dimension. This strategy has been useful in providing a nomenclature of the pattern of cognitive impairment those patients experience. However, it does not provide information regarding the dynamic of the brain-behavior relationship as the brain looses healthy neurons. This might be a major shortcoming because the recent literature on brain plasticity suggests that cerebral insult results in substantial plasticity and reorganization even in the aging brain [2, 3]. Because lesions are progressive, the AD brain might attempt neural compensatory mechanisms, particularly during the first stages of the disease while it still has sufficient resources and these might be successful. If true, disease severity should have a profound impact on the pattern of functional activation associated with different cognitive tasks. The major goal of this study was to provide the empirical data to address this important question.

The idea that the functional brain activation changes as the brain acquires more pathology in neurodegenerative diseases is contained in a number of integrative models of cerebral activation [4-7]. For example, Prvulovic and collaborators [8] have suggested that the brain damage characteristic of the earliest phase of AD decreases processing efficiency in mildly affected brain areas while preserving their processing capacity. As a result, regions that are only mildly impaired should have sufficient neuronal resources to allow the implementation of compensatory mechanisms relying on increased neuronal

recruitment and brain activation. This would result in the hyperactivation of mildly affected brain regions in patients relative to controls when compared using functional brain imaging techniques. However, as the disease advances, increasing damage to the affected brain regions results in a decrement in processing efficiency and capacity, impeding neuronal recruitment and compensatory mechanisms. This inability to compensate should be associated with hypoactivation. The pattern of brain functional activation in AD may therefore be characterized by a dynamic shift from normal to hyper- to hypoactivation as the disease progresses and extends to different brain areas. There are also predictions regarding the brain areas that should reflect hyper and hypoactivation. In the early compensation phase, hyperactivation should be found in areas that are mildly affected by the disease and that are typically recruited by the cognitive task. It is also expected that hyperactivation occur in alternative areas that might be used to support compensation [9, 10]. Later in the disease, hypoactivation should be found in disease-affected areas that are recruited for the cognitive task. This dynamic view of brain activation in neurodegenerative diseases holds considerable promise for understanding severity-related activations in AD.

Our predictions are expected to be particularly relevant for brain activations related to episodic memory, as it is one of the first cognitive functions to be impaired in early AD [11, 12] and the main domain of subjective cognitive complaints [13]. The neural substrates of episodic memory have been studied extensively [see 14, for a review], but very little is known about how these memory networks are modified as the brain acquires new pathologies. Furthermore, and as mentioned above, neural compensation depends not only on disease severity, but also on the task demands and

characteristics. As different components are impaired at different phases during the disease, they should benefit differently from compensation during the course of their progression. This is relevant here as different components of episodic memory retrieval are dependent on different brain regions and thus impaired in different sequences during the disease process. This is the case with recollection, which refers to the retrieval of the event/item with its context of encoding, and with familiarity, which refers to the recognition that the event/item is experienced but without its contextual details. Accordingly, it has been suggested that associative recognition, which is mostly based on recollection processes, is altered in persons with mild cognitive impairment (MCI), whereas item recognition, which is mostly based on familiarity processes, is impaired later, when persons meet criteria for AD [15-17; but see 18]. The model predicts that the extent of damage in a process-related network will determine its potential for compensation. Compensation will only surface when damage is present but the damage need be mild to support compensation. Thus, it can be predicted that persons with less severe MCI will show more neural compensation for associative recognition than for item recognition because the associative recognition network is vulnerable at this stage and lesions are mild enough to allow brain plasticity to occur. By contrast, persons with more severe MCI should show neural compensation only for item-recognition because impairment to the associative recognition network is too severe to allow compensation (Figure 1).

The predictions were tested using a median split of Mattis Dementia Rating Scale (MDRS) scores to divide degrees of MCI. The assumption was that individuals with lower scores were in a more advanced phase of the disease and/or experienced a larger

degree of brain pathology than persons with higher scores. We tested the effect of severity on brain activation and compensation using a word-pair associative recognition procedure with two retrieval conditions: an item recognition and an associative recognition. We predicted that persons with milder MCI would show neural compensation during associative recognition only, whereas those with more severe MCI would show neural compensation during item recognition only. In terms of brain activation, these neural compensatory mechanisms were predicted to manifest as hyperactivation (i.e., more activation than healthy controls) in key regions involved in episodic memory retrieval and possibly in remote brain areas that have been identified as being involved in memory-related compensatory mechanisms in older adults. For instance, prefrontal regions controlateral to the ones usually activated by episodic memory tasks have been identified as compensatory structures in "high-performing" older adults [19]. Also, the dorsolateral prefrontal cortex is known to increase its activation following attentional training in healthy older adults, suggesting an involvement of this area in compensatory mechanisms [20]. A shift from hyperactivation (see Figure 1) associated with a memory process affected early (associative recognition) to hyperactivation associated with a memory process affected later (item recognition) would reflect the compensation breakdown for associative retrieval and emergence of compensation for item retrieval during the MCI phase. Thus, plastic changes are predicted to involve different cognitive processes as brain dysfunction develops in MCI. Investigating the relationship between cognitive severity and fMRI brain activation pattern in this population will provide crucial new information regarding the dynamic nature of the brain/behavior relationship and will allow a better understanding of

compensatory mechanisms in age-related cognitive disorders.

Materials and Methods

Participants

Forty participants, 26 persons with MCI and 14 healthy older adults, took part in this study. Participants with MCI were recruited from memory clinics and met the criteria for single- or multiple-domain amnestic MCI [11, 21, 22]: (1) they expressed a concern regarding their memory; (2) they performed at least 1.5 standard deviation (SD) below the average level of persons of similar age and education on standardized memory tests; (3) they showed no global cognitive impairment on the basis of the Mini-Mental State Examination (MMSE, adjusted for age and education); and (4) they showed no significant impact on daily functions as measured by the SMAF (Functional Autonomy Measurement System) functional impairment scale and clinical interview. Persons with MCI completed an extensive neuropsychological evaluation that covered episodic memory [Rappels Libres/Rappels indicés-16, RL/RI-16, free and cued word recall task, 23, 24; Batterie d'Efficience Mnésique, BEM, text memory, 25; and 20-min recall of the Rey's Complex Figure, 26], executive functions [third plate of Stroop-Victoria, 27; and copy of Rey's Complex Figure, 26], visuospatial processing [Benton Judgment of line orientation, 28], speed of information processing [Coding of the WAIS-III, 29], language [Boston Naming Test, 30], and global cognitive functions [Mattis Dementia Rating Scale, MDRS, 31; and Mini-Mental State Examination, MMSE, 32]. Participants with MCI also underwent an extensive medical, neurological, and neuroradiological examination to exclude the presence of any other significant systemic, neurological, or psychiatric condition that could explain their cognitive difficulties.

A median split of the MDRS [31] scores was used to separate participants with MCI into two groups: those with a higher level of overall cognitive functioning (MCI higher-cognition, n = 13) and those with a lower level of overall cognitive functioning (MCI lower-cognition, n = 13). The MDRS was preferred over the MMSE [32] as a measure of severity because participants with MCI show less of a ceiling effect on this scale; thus, it has the variability necessary to use a median split. In addition, the MDRS may be more sensitive to the milder cognitive impairments of those with MCI, as it investigates a broader range of cognitive functions.

Participants with MCI were followed over a two-year period after their participation in this study. At the two-year follow-up, no one in the MCI higher-cognition group met criteria for AD. Of the same group, seven had remained stable, and six showed a cognitive decline insufficient to meet criteria for AD. Over the same period, four in the MCI lower-cognition group remained stable, one showed cognitive decline insufficient for AD, and eight were diagnosed with AD. Patients with AD were diagnosed according to the NINCDS-ADRDA [33] and DSM-IV criteria [34].

Healthy older adults also completed an abbreviated clinical and neuropsychological assessment involving measures of global cognitive functions (MDRS,[3] MMSE), speed of information processing [Coding subtest of the WAIS-III, 29], and episodic memory [a cued and free word recall task: RL/RI-16, 23] to ensure they did not suffer from cognitive deficits. The study was approved by an ethics committee: le

[3] Five healthy controls did not undergo the MDRS.

Comité mixte d'éthique de la recherche du Regroupement Neuroimagerie/Québec (CMER-RNQ).

Data acquisition

Magnetic resonance imaging was performed using a SIEMENS 3T Magnetom TRIO System (Erlangen, Germany) at the Unité de Neuroimagerie Fonctionnelle (UNF) of the Institut Universitaire de Gériatrie de Montréal. For high anatomical resolution, a sagittal T1-weighted three-dimensional MPRAGE sequence was obtained at the end of the two runs (TR/TE = 1950/3.93 ms, flip angle = 15 °; 176 slices, voxel size = 1 × 1 × 1 mm, field of view = 256 mm, matrix = 256 × 256). Functional MR images were acquired using gradient-echo echo-planar imaging sequences (GE-EPI) sensitive to blood oxygen level-dependent (BOLD) contrast (TR/TE = 2000/30 ms, flip angle= 90 °; 31 interleaved slices, voxel size = 3.75 × 3.75 × 5 mm with a gap of 1 mm, field of view = 240 mm, matrix = 64 × 64).

Task procedure

Participants were first asked to memorize 16 lists of nine concrete word pairs consisting of one or two syllables. Half of the word pairs were semantically related pairs of words (e.g., butter–cheese), and the other half were semantically unrelated pairs (e.g., tire–game). Related pairs were created by selecting an item and one of its associates from French lists of semantic associates [35, 36]. Only the second, third, or fourth associates of selected words were chosen to avoid participants guessing and to avoid the encoding of the two words as a single concept. Lists of unrelated word pairs were created by selecting pairs of words with no semantic relation and by ensuring that no words were

semantically associated with other items in the list. All 16 lists were matched in terms of word frequency and word length.

Recognition was then tested by asking participants to perform a yes/no recognition judgment. Two recognition conditions were tested, each with eight lists of word pairs. In the *old/new judgment* condition, each of the lists was composed of four old pairs of words (the same pair presented during the encoding phase; e.g., tire–game, from the above example) and four new pairs of words (one word presented during the encoding phase and one completely new word; e.g., cheese–milk from the above example) arranged in random order. Of the eight word pairs, half were presented in the same format as during the study phase (e.g., tire–game), and the other half were presented in a reversed format (e.g., game–tire) to ensure participants did not learn only the second word to achieve the task. In the *intact/rearranged judgment* condition, each of the lists was composed of four intact pairs of words (the same pair presented during the encoding phase; e.g., butter–cheese from the above example) and four rearranged pairs of words (two words presented during the encoding phase but belonging to two different pairs; e.g., butter–tire from the above example) arranged in random order. Again, half of the word pairs were presented in the same format as during the encoding phase (e.g., butter–cheese), and the other half were presented in a reversed format (e.g., cheese–butter). To prevent participants from retrieving items from their short-term memory, at least four word pairs separated the presentation of a pair in the study phase from its presentation in the recognition phase. All lists were equivalent in terms of word frequency and semantic relatedness.

fMRI procedure

The task was programmed on E-prime, and stimuli were visually presented and mirror projected. Goggles appropriate for MRI scanning were used to correct the vision of the subjects when needed. An fMRI block design paradigm was preferred over an event-related one to maximize detection power [37] and to be more suitable for patients with memory difficulties, as the conditions alternate less frequently in a block design. Subjects performed the memory task in two runs, each composed of four alternating series of visual fixation (20 s; fixation of a crosshair), encoding (40 s; memorization of nine visually presented pairs of words per block), and recognition (44 s; recognition judgment of eight visually presented pairs of words per block). During the study phase, word pairs were visually presented at a rate of 4 s per pair and mirror projected to participants while they were in the fMRI scanner. Note that brain activation was recorded during the study phase and that data are being reported in a separate paper [38]. It was found that MCI higher-cognition showed hyperactivations in prefrontal areas whereas the MCI lower-cognition did not show these hyperactivations and even showed hypoactivations in posterior regions. During the recognition phase, word pairs were visually presented at a rate of 5 s per pair. Each recognition block consisted of either only old/new judgment or only intact/rearranged judgment. In addition, brief instructions (4 s) were presented to subjects, prior to each recognition block, telling them to indicate on a two-button response box whether the complete pair had been seen in the study phase. Emphasis was placed on the fact that a positive answer should be provided when the two words were seen as a pair. These instructions were the same for the two recognition conditions. Thus, a “yes” response would be provided for old (in the old/new condition) and intact (in the intact/rearranged condition) pairs, and a “no” response would be

provided for new (in the old/new condition) and rearranged (in the intact/rearranged condition) pairs. The order of presentation of the old/new lists and the intact/rearranged lists was randomized and fixed across participants. One week prior to scanning, participants were familiarized with the fMRI procedure and the tasks, using a simulator that mimics the entire fMRI environment.

Image processing and data analysis

Before statistical analysis, functional images were converted into Analyze format and unwarped. Functional volumes from each subject were then realigned to the first acquired volume in the session, and a mean realigned volume was created for each subject. All the realigned volumes from each subject were spatially normalized into Montreal Neurological Institute (MNI) stereotactic space and spatially smoothed with an 8-mm Gaussian kernel. Low-frequency noise was removed with a high-pass filter of 208 s. The instruction blocks were modeled as a condition of no interest. A single-subject analysis was carried out to evaluate the individual contrasts (old/new judgment vs. visual fixation, intact/rearranged judgment vs. visual fixation) for each subject. A random effect (RFX) analysis was then performed on the contrast images with a two-way analysis of covariance (ANCOVA) using Group (healthy older adults, MCI higher-cognition, MCI lower-cognition) as a between-subject factor and Condition (old/new judgment, intact/rearranged judgment) as a within-subject factor, with non-sphericity correction, replications over subjects, and correlated repeated measures. Also, the mean performance (%) of each subject on the task was used as a covariate (see below). T-tests were thus performed on the contrast of each task (Recognition old/new > visual fixation & Recognition intact/rearranged > visual fixation) for each group individually (within-

group analyses) as well as between the groups (between-group analyses). In addition, t-tests were performed between the old/new condition and the intact/rearranged condition for the healthy control group. Within-group analyses were performed using a threshold of $p < .05$, family-wise corrected (FWE) with 10 contiguous voxels. Between-group analyses were performed with a more liberal threshold of $p < .001$ (uncorrected, with 5 contiguous voxels) in accordance with what has been used most frequently in the MCI fMRI literature [e.g., 39-42]. All preprocessing and statistical analyses were performed in MATLAB 7.0 (http://www.mathworks.com) using the statistical parametric mapping software SPM5 (http://www.fil.ion.ucl.ac.uk/spm/).

Results

Sociodemographic and clinical data

Table 1 shows the sociodemographic data and the results of the neuropsychological evaluation for all three groups. The MDRS score of MCI participants (ranged from 117 to 144, mean = 134.61, SD = 6.03, skewness = -.81) was used to assign each MCI person to either the MCI higher- or lower-cognition groups. One-way ANOVAs with Group (healthy controls, MCI higher-cognition, MCI lower-cognition) as a between-subject factor indicated the groups did not differ in age ($F_{(2,37)} = 0.15$, NS) or education ($F_{(2,37)} = 0.64$, NS). In addition, chi-square analyses indicated a similar male-to-female ratio in the three groups ($\chi^2 = 0.05$, $\chi^2 = 0.03$ and $\chi^2 = 0.16$ for the comparison between healthy controls and MCI higher-cognition, healthy controls and MCI lower-cognition, and MCI higher-cognition and MCI lower-cognition, respectively, all NS).

One-way ANOVAs with Group (healthy controls, MCI higher-cognition, MCI lower-cognition) as a between-subject factor were also computed on cognitive measures

followed by Tukey's post hoc test to determine the source of the effect (Table 1). As expected, both MCI groups showed lower episodic memory capacities than healthy controls (i.e. lower score on the RL/RI-16 test for both groups and lower score on the delayed recall of Rey's Figure for the MCI lower-cognition group), and MCI lower-cognition showed lower episodic memory performances than MCI higher-cognition.

The number of persons meeting criteria for single- or multiple-domain amnestic MCI was also compared across groups. The MCI higher-cognition group comprised five persons with single-domain amnestic MCI and eight persons with multiple-domain amnestic MCI, whereas the MCI lower-cognition group comprised four persons with single-domain amnestic MCI and nine with multiple-domain amnestic MCI. These numbers were equivalent ($\chi^2 = 0.17$, NS).

Behavioral data

The behavioral data obtained from the recognition test are illustrated in Figure 2. A two-way ANOVA with Group (healthy controls, MCI higher-cognition, MCI lower-cognition) as a between-subject factor and Condition (old/new judgment, intact/rearranged judgment) as a within-subject factor was computed using the mean percentage of correctly recognized pairs as a dependent variable. A Group effect ($F_{(2,37)} = 9.87$, $p < .001$) and a Condition effect ($F_{(1,37)} = 79.35$, $p < .001$) were observed. Tukey's post hoc test showed that healthy controls and persons in the MCI higher-cognition group recognized more word pairs than those in the MCI lower-cognition group ($p < .001$ for both groups), but that the healthy control and MCI higher-cognition groups did not differ from each other. In addition, the Condition effect was due to all three groups performing worse on the intact/rearranged judgment condition than on the

old/new judgment condition. No Group-by-Condition interaction was found. Because both Group and Condition showed a significant effect on performance level, all fMRI analyses were computed using individual performance scores as a covariate. All analyses were also performed without the covariate. This resulted in a slight decrease in the amount of regions that showed significant activation. However, it did not change the general pattern of results.

Hit rates, false alarms and an index of sensitivity (d' = Z(hit rates) – Z(false alarms) were also computed. Healthy controls showed a mean hit rate of 0.84 (SD = 0.23), a mean false alarm rate of 0.09 (SD = 0.12) and a d' of 3.34 (SD = 1.47) for item recognition. MCI higher-cognition showed a mean hit rate of 0.78 (SD = 0.26), a mean false alarm rate of 0.20 (SD = 0.22) and a d' of 2.42 (SD = 1.09) for item recognition. MCI lower-cognition showed a mean hit rate of 0.64 (SD = 0.28), a mean false alarm rate of 0.43 (SD = 0.23) and a d' of 0.82 (SD = 0.87) for item recognition. For the associative recognition task, healthy controls showed a mean hit rate of 0.79 (SD = 0.21), a mean false alarm rate of 0.38 (SD = 0.21) and a d' of 1.33 (SD = 0.77). MCI higher-cognition showed a mean hit rate of 0.77 (SD = 0.25), a mean false alarm rate of 0.42 (SD = 0.29) and a d' of 1.28 (SD = 1.39) for associative recognition. MCI lower-cognition showed a mean hit rate of 0.58 (SD = 0.31), a mean false alarm rate of 0.55 (SD = 0.36) and a d' of 0.10 (SD = 0.97) for associative recognition.

fMRI data

Within-group comparisons

Item recognition. The areas of activation for the old/new judgment condition are presented in Table 2 and Figure 3 for the three groups separately. In this condition, all groups showed activation in the left inferior and superior parietal lobules and the precuneus (BA 7, 39, and/or 40), the occipital lobe on both sides (BA 17, 18, and/or 19), the right medial prefrontal cortex and cingulate cortex (BA 8, 32) and the left Broca's area (BA 44). In addition to these common areas of activation, healthy controls showed activation in the right cerebellum and the left dorsolateral prefrontal cortex (BA 46). In the MCI higher-cognition group, the condition was associated with additional areas of activation in the right inferior parietal lobule (BA 39, 40), the left medial prefrontal and anterior cingulate cortex (BA 8, 24, and/or 32), the left premotor area (BA 6), the left precentral and postcentral gyri (BA 2, 3, and/or 4), the left ventrolateral prefrontal cortex (BA 45, 47), the right ventrolateral prefrontal cortex (44, 45, 47), and the right dorsolateral prefrontal cortex (BA 46). In addition to the common areas of activation mentioned above, the MCI lower-cognition group showed areas of activation in the right cerebellum, the inferior parietal lobule bilaterally (BA 39, 40), the medial prefrontal and anterior cingulate cortex bilaterally (BA 8, 24, and/or 32), the premotor area bilaterally (BA 6), the left precentral and postcentral gyri (BA 2, 3, and/or 4), the ventrolateral prefrontal cortex bilaterally (BA 44, 45, 47 and the left dorsolateral prefrontal cortex (BA 46).

Associative recognition. The areas of activation for the intact/rearranged judgment condition are presented in Table 3 and Figure 3 for the three groups separately. This condition was associated with activation in the left occipital lobe (BA 17, 18, and/or 19) and the right medial prefrontal cortex and cingulate cortex (BA 8, 32) in all three

groups. Healthy controls also showed areas of activation in the left and right inferior and superior parietal lobules and the precuneus (BA 7, 39, and/or 40), the left Broca's area (BA 44), the left premotor area (BA 6), and the left medial prefrontal cortex and cingulate cortex (BA 8, 32). The MCI higher-cognition group also showed areas of activation in the left and right inferior and superior parietal lobules and the precuneus (BA 7, 39, and/or 40), the left Broca's area (BA 44), the left premotor area (BA 6), the left and right dorsolateral prefrontal cortices (BA 9, 46), the right ventrolateral prefrontal cortex (BA 44, 45, 47), the left ventrolateral prefrontal cortex (BA 45, 47), the left motor postcentral and precentral gyri (BA 3, 4), and the right cerebellum. The MCI lower-cognition group did not recruit additional regions during this condition.

Between-group comparisons

Between-group comparisons were performed to directly compare the differences in activation as a function of the recognition condition between the two MCI groups and the healthy control group. The data is reported in Table 4 and Figure 4.

MCI higher-cognition vs. healthy controls. In the intact/rearranged condition (associative recognition), analyses indicated a number of brain areas with more activation in persons in the MCI higher-cognition group than in healthy controls. More activation was found in the left inferior parietal lobule (BA 40), the right temporal lobe (BA 37, 41), the left and right dorsolateral prefrontal cortices (BA 9), and the right ventrolateral prefrontal cortex (BA 44). During the old/new condition (item recognition), no area showed significantly more activation in the MCI higher-cognition group than in healthy controls. The only significant differences associated with item-recognition between these two groups were found in the right posterior cingulate cortex and parahippocampal

gyrus, where more activation was found in healthy controls than in persons in the MCI higher-cognition group. Areas of hyperactivation were thus found exclusively for associative recognition in MCI higher-cognition.

MCI lower-cognition vs. healthy controls. In the intact/rearranged condition (associative recognition), no areas showed more activation in the MCI lower-cognition group than in healthy controls. By contrast, the old/new condition (item recognition) was associated with more activation in MCI lower-cognition than in healthy controls in many areas including the left dorsolateral prefrontal cortex (BA 46), the medial prefrontal cortex bilaterally (BA 8), the left inferior parietal lobule (BA 40), and the anterior cingulate cortex bilaterally (BA 24, 32). Areas of hyperactivation were thus found exclusively for item recognition in the MCI lower-cognition group.

MCI higher-cognition vs. MCI lower-cognition. The only significant difference of activation between the two MCI groups was observed in the precuneus and superior parietal lobule (BA 7) bilaterally where MCI higher-cognition had more activation than MCI lower-cognition during the intact/rearranged condition. No other differences were found.

Between-task comparison

Between-task comparisons were performed in healthy controls to highlight the regions that are specifically more activated by each task. The data is reported in Table 5. Healthy controls showed more activation during the old/new condition than in the intact/rearranged condition in the medial prefrontal cortex bilaterally (BA 10), in the

parahippocampal gyri bilaterally, and in the right middle and superior temporal gyrus (BA 19, 39). In contrast, they showed more activation during the intact/rearranged condition than in the old/new condition in the left basal ganglia and in the right anterior cingulate cortex (BA 24).

Discussion

This paper assessed the effect of disease severity on the dynamic of compensatory brain plasticity in individuals with MCI. Scores on the MDRS reflected the degree of participants' global cognitive functioning, whereas an old/new judgment and an intact/rearranged judgment measured item and associative recognition, respectively. Our model predicts that disease severity would have a different effect on brain activation depending on the cognitive process: Individuals with less severe MCI were expected to show neural compensation for associative recognition only, whereas those with more severe MCI were expected to show neural compensation for item recognition only. Results support this hypothesis (Figure 4): during the milder stage, MCI persons recruit additional brain areas during demanding recognition condition (i.e., associative recognition) while showing fairly similar brain activations to that of healthy controls on a less demanding condition (i.e. item recognition). This indicates that the brain areas underlying item recognition are not yet significantly affected by the disease. However, as MCI individuals progress in the disease, they experience a shift in their brain activation pattern: Recruitment of the compensation network for associative recognition is dismissed, but a network of brain areas, similar to the compensatory network used by the MCI higher-cognition group during associative recognition, is hyperactivated during item recognition. We therefore found a shift in hyperactivation (see Figure 1) from

associative to item recognition as a function of disease severity, suggesting a compensation breakdown for associative retrieval and emergence of compensatory mechanisms for item retrieval.

This shift in hyperactivation is in agreement with the neurodegenerative fMRI model proposed by Prvulovic and collaborators [8] and with recent data that show a similar compensation breakdown in individuals with more severe MCI for the encoding of information [43]. As predicted, many of the regions that showed hyperactivation in the two MCI subgroups were located in key regions for episodic memory retrieval (i.e., the right dorsolateral and ventrolateral prefrontal cortices and the left inferior parietal lobule) [see 14]. This larger recruitment in regions specialized for memory processes probably reflects the fact that brain regions affected by the disease need to increase their activation to optimize performance. However, we also observed additional activations in regions that are usually not reported as being involved in those verbal episodic tasks. Those additional zones of activations were located in regions contralateral to areas typically activated in verbal episodic memory tasks (i.e., the left dorsolateral prefrontal cortex, the right temporal lobe). These new activations may represent the recruitment of additional compensatory networks, which is also reflected by a direct comparison between the two MCI subgroups that has revealed that MCI higher-cognition show more activation in posterior regions than MCI lower-cognition during associative recognition. These areas have been shown to accumulate an increased level of amyloid deposition, as measured with positron emission tomography with Pittsburgh's Compound B, in AD patients [44, 45].

It must be noted that our fMRI analyses were covaried for performance level since the performances of the MCI lower-cognition group were lower than the ones of the two other groups. Thus, group differences in activation cannot be related to mere differences in degrees of effort on the task. This is an important issue, as it has been shown that performance level explains most of the differences in brain activation between healthy controls and patients with AD [46]. Importantly, a similar pattern of results was found when repeating our analyses without covarying for performance, suggesting that our findings reflect an intrinsic difference in the neural networks of our participants rather than a simple effect of performances on brain activation.

Behavioral results indicate impaired associative recognition and item recognition in persons in the MCI-lower cognition group, but preserved performance in those in the MCI higher-cognition group. Although many studies have found intact item or familiarity-based recognition in MCI [15-17], the contrary has been observed in one study [18]. Our results point to a possible explanation for the divergent findings in the literature: The different levels of severity in the MCI groups may explain the different levels of impairment on the associative and item recognition tasks. It may also appear surprising that the MCI higher-cognition group performed at the same level as the healthy controls on the experimental tasks even though they met criteria for MCI and were thus impaired on the more classical neuropsychological tests such as the free and cued word recall task and text memory task. This can probably be explained by the fact that the clinical neuropsychological evaluation of memory relied on free recall, whereas that of experimental tasks used recognition. The current literature is rather controversial regarding this issue, but some studies have reported a preservation of recognition

memory in MCI [47-50]. Another possible explanation is disease severity, as those studies reporting preserved recognition relied on MCI participants who were slightly less impaired (mean MMSE of 27.5 and 27.0, respectively) than those reporting impaired recognition (mean MMSE of 26.1 and 26.4, respectively). Accordingly, in this study, individuals with less severe MCI (mean MMSE of 28.85) showed preserved recognition, whereas those with more severe MCI (mean MMSE of 26.46) showed impaired recognition.

Another finding relates to the activation of the prefrontal cortex, which tended to be more bilaterally activated in both MCI groups than in healthy controls. MCI higher-cognition showed bilateral activation of many prefrontal regions during both the old/new condition (BA 6, 44, 45, 47) and the intact/rearranged condition (BA 9, 44, 46), whereas the MCI lower-cognition showed bilateral activation during the old/new condition only (BA 44, 45, 47). This bilateral activation is in agreement with recent models that highlight the importance of interhemispheric interaction in neural compensatory mechanisms [9, 10]. Similarly, the left inferior parietal lobule (BA 40) appears to be a key component of the compensatory network used during MCI, as it showed hyperactivation in the MCI higher-cognition group during the intact/rearranged condition and in the MCI lower-cognition group during the old/new condition. The involvement of the left lateral parietal lobe in memory retrieval is in line with data reported in previous studies [see 51, for a review] and is often interpreted as reflecting attentional processes directed at internal mnemonic representations. Thus, it is plausible that one of the compensatory mechanisms used by individuals with MCI involves allocating increased attentional resources to the memory task.

The present study does have some limitations. First, the design was cross-sectional and therefore did not directly measure the MCI-to-AD continuum. A related limitation concerns the possibility that some of the individuals with MCI were not in a prodromal phase of AD. Note, however, that 58% of the individuals with MCI in our study either showed cognitive decline or progressed to AD after only two years, suggesting that a large proportion of those participants may be on a pathological pathway. A third potential limitation is our use of a block fMRI design rather than an event-related design. One pitfall of the block design is that it does not allow a comparison between correct and incorrect responses. However, this design is more suitable for patients with memory difficulties, as the conditions alternate less frequently, and offers maximal detection power [37]. The power issue was particularly critical in our context, as we were looking for differences related to severity levels likely to yield more modest effect sizes than when comparing a clinical with a control group. Furthermore, blocked design might allow us to interpret our tasks as reflecting the "retrieval mode" in which participants are engaged in during the recognition phase [52-54]. Also, the use of a clinical measure (i.e., MDRS) as an indicator of disease severity may not be ideal. We favored a measure of global cognitive performance because it is closer to the current criteria for identifying MCI and AD than are neuroanatomical markers. It is noteworthy that the MDRS scores for individuals with MCI correlated strongly with their performances on the RL/RI-16 3rd free recall ($r = 0.68$, $p < .001$) and delayed free recall ($r = 0.71$, $p < .001$) tasks. This supports our contention that using this score as a measure of disease severity is sound.

Overall, the findings of this study point toward the presence of neural compensation and brain plasticity throughout the entire phase of MCI. However, this phase does feature a change in the pattern of neural compensation (Figure 4). At first, persons with MCI recruit a large network of additional brain areas during the most demanding recognition condition (i.e., associative recognition), and this is accompanied by a normal performance level. During this early phase, item recognition is unimpaired behaviorally and is associated with fairly similar brain activation to that of healthy controls, probably reflecting that the brain areas underlying item recognition are not yet affected by the disease. Therefore, item recognition can be judged to be truly unimpaired. As individuals with MCI progress in the disease, they experience a shift in their pattern of neural compensation: Recruitment of the compensation network for associative recognition is dismissed, but a network of brain areas, similar to the compensatory network used by the MCI higher-cognition group during associative recognition, is hyperactivated while completing a task that taps item recognition, a less demanding cognitive process. This shift in hyperactivation reveals a breakdown in the compensatory mechanisms for associative retrieval during the MCI phase, with gradual emergence of compensation for item retrieval.

Acknowledgement

This work was supported by a grant from Canadian Institutes of Health Research (CIHR) to SB. SB received a National Research Award from the Fonds de la Recherche en Sante du Quebec (FRSQ) and FC was supported by a doctoral scholarship from CIHR. We thank Émilie Lepage, Fanny-Maude Urfer, and Rosalie Perron for the neuropsychological evaluation of the participants, the clinical neuropsychology service of the IUGM (Chief, Francine Fontaine, Ph.D) for their contribution to the interpretation of test results, Dr Serge Gauthier, Dr Christian Bocti and the IUGM cognition clinic (Director: Dr Marie-Jeanne Kergoat) for MCI referral, Samira Mellah for assistance in task construction and data collection, and Harold Gaboury for editorial assistance.

References

[1] Bennett DA, Wilson RS, Schneider JA, Evans DA, Beckett LA, Aggarwal NT, Barnes LL, Fox JH, Bach J (2002) Natural history of mild cognitive impairment in older persons. *Neurology* **59**, 198-205.

[2] Grady CL (2008) Cognitive neuroscience of aging. *Ann N Y Acad Sci* **1124**, 127-144.

[3] Rajah MN, D'Esposito M (2005) Region-specific changes in prefrontal function with age: a review of PET and fMRI studies on working and episodic memory. *Brain* **128**, 1964-1983.

[4] Friston KJ, Price CJ (2003) Degeneracy and redundancy in cognitive anatomy. *Trends Cogn Sci* **7**, 151-152.

[5] Price CJ, Friston KJ (2002) Degeneracy and cognitive anatomy. *Trends Cogn Sci* **6**, 416-421.

[6] Rapoport SI, Grady CL (1993) Parametric in vivo brain imaging during activation to examine pathological mechanisms of functional failure in Alzheimer disease. *Int J Neurosci* **70**, 39-56.

[7] Wermke M, Sorg C, Wohlschlager AM, Drzezga A (2008) A new integrative model of cerebral activation, deactivation and default mode function in Alzheimer's disease. *Eur J Nucl Med Mol Imaging* **35 Suppl 1**, S12-24.

[8] Prvulovic D, Van de Ven V, Sack AT, Maurer K, Linden DE (2005) Functional activation imaging in aging and dementia. *Psychiatry Res*. **140**, 97-113.

[9] Banich MT (1998) The missing link: the role of interhemispheric interaction in attentional processing. *Brain Cogn* **36**, 128-157.

[10] Cabeza R (2002) Hemispheric asymmetry reduction in older adults: the HAROLD model. *Psychol Aging* **17**, 85-100.

[11] Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E (1999) Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol* **56**, 303-308.

[12] Perri R, Serra L, Carlesimo GA, Caltagirone C (2007) Amnestic mild cognitive impairment: difference of memory profile in subjects who converted or did not convert to Alzheimer's disease. *Neuropsychology* **21**, 549-558.

[13] Clement F, Belleville S, Gauthier S (2008) Cognitive complaint in mild cognitive impairment and Alzheimer's disease. *J Int Neuropsychol Soc* **14**, 222-232.

[14] Cabeza R, Nyberg L (2000) Imaging cognition II: An empirical review of 275 PET and fMRI studies. *J Cogn Neurosci* **12**, 1-47.

[15] Westerberg CE, Paller KA, Weintraub S, Mesulam MM, Holdstock JS, Mayes AR, Reber PJ (2006) When memory does not fail: familiarity-based recognition in mild cognitive impairment and Alzheimer's disease. *Neuropsychology* **20**, 193-205.

[16] Anderson ND, Ebert PL, Jennings JM, Grady CL, Cabeza R, Graham SJ (2008) Recollection- and familiarity-based memory in healthy aging and amnestic mild cognitive impairment. *Neuropsychology* **22**, 177-187.

[17] Hudon C, Belleville S, Gauthier S (2009) The assessment of recognition memory using the Remember/Know procedure in amnestic mild cognitive impairment and probable Alzheimer's disease. *Brain Cogn* **70**, 171-179.

[18] Wolk DA, Signoff ED, Dekosky ST (2008) Recollection and familiarity in amnestic mild cognitive impairment: a global decline in recognition memory. *Neuropsychologia* **46**, 1965-1978.

[19] Cabeza R, Anderson ND, Locantore JK, McIntosh AR (2002) Aging gracefully: Compensatory brain activity in high-performing older adults. *Neuroimage* **17**, 1394-1402.

[20] Erickson KI, Colcombe SJ, Wadhwa R, Bherer L, Peterson MS, Scalf PE, Kim JS, Alvarado M, Kramer AF (2007) Training-induced functional activation changes in dual-task processing: an FMRI study. *Cereb Cortex* **17**, 192-204.

[21] Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV, Ritchie K, Rossor M, Thal L, Winblad B (2001) Current concepts in mild cognitive impairment. *Arch Neurol* **58**, 1985-1992.

[22] Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, Nordberg A, Backman L, Albert M, Almkvist O, Arai H, Basun H, Blennow K, de Leon M, DeCarli C, Erkinjuntti T, Giacobini E, Graff C, Hardy J, Jack C, Jorm A, Ritchie K, van Duijn C, Visser P, Petersen RC (2004) Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *J Intern Med* **256**, 240-246.

[23] Buschke H (1984) Cued recall in amnesia. *Journal of Clinical Neuropsychology* **6**, 433-440.

[24] Van der Linden M, Adam S, Agniel A, Baisset-Mouly C, Bardet F, Coyette F, Desgranges B, Deweer B, Ergis AM, Gély-Nargeot MC, Grimomprez L, Juillerat AC, Kalafat M, Poitrenaud J, Sellal F, Thomas-Antérion C (2004) *L'évaluation*

de troubles de la mémoire: présentation de quatre tests de mémoire épisodique (avec étalonnage), Solal, Marseille.

[25] Signoret JL (1991) *Batterie d'efficience mnésique BEM 144*, Elsevier, Paris.

[26] Rey A (1959) *Test de copie d'une figure complexe: manuel*, Les éditions du centre de psychologie appliquée, Paris.

[27] Regard M (1981) (University of Victoria, Canada).

[28] Benton AL, Hamsher K, Varney NR, Spreen O (1983) *Contributions to neuropsychological assessment*, Oxford University Press, New York.

[29] Wechsler D (1997) *Wechsler Adult Intelligence Scale-III* Psychological Corporation, New York.

[30] Kaplan EF, Goodglass H, Weintraub S (1983) *The Boston Naming Test (2nd edition)*, Lea & Febiger, Philadelphia, PA.

[31] Mattis S (1976) Mental status examination for organic mental syndrome in the elderly patient In *Geriatric Psychiatry*, Bellak L, Karasu TB, eds. Grune & Stratton, New York, pp. 77–121.

[32] Folstein MF, Folstein SE, McHugh PR (1975) Mini-Mental State: A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research* **12**, 189-198.

[33] McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984) Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* **34**, 939-944.

[34] American Psychiatric Association (2000) *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*, American Psychiatric Publishing, Inc.

[35] Freibergs V (1968) *Normes d'association libre aux 100 mots Kent-Rosanoff*

[36] Freibergs V (1970) *Normes d'association libre aux premières cinq réponses des hiérarchies d'associations aux 100 mots Kent-Rosanoff*

[37] Liu TT (2004) Efficiency, power, and entropy in event-related fMRI with multiple trial types. Part II: design of experiments. *Neuroimage* **21**, 401-413.

[38] Clement F, Belleville S (2010) Compensation and disease severity on the memory-related activations in mild cognitive impairment. *Biol Psychiatry* **68**, 894-902.

[39] Kircher T, Weis S, Freymann K, Erb M, Jessen F, Grodd W, Heun R, Leube DT (2007) Hippocampal activation in MCI patients is necessary for successful memory encoding. *J Neurol Neurosurg Psychiatry* **78**, 812-818.

[40] Sole-Padulles C, Bartres-Faz D, Junque C, Vendrell P, Rami L, Clemente IC, Bosch B, Villar A, Bargallo N, Jurado MA, Barrios M, Molinuevo JL (2007) Brain structure and function related to cognitive reserve variables in normal aging, mild cognitive impairment and Alzheimer's disease. *Neurobiol Aging (2007), doi:10.1016/j.neurobiolaging.2007.10.008*.

[41] Heun R, Freymann K, Erb M, Leube DT, Jessen F, Kircher TT, Grodd W (2007) Mild cognitive impairment (MCI) and actual retrieval performance affect cerebral activation in the elderly. *Neurobiol Aging* **28**, 404-413.

[42] Ries ML, Schmitz TW, Kawahara TN, Torgerson BM, Trivedi MA, Johnson SC (2005) Task-dependent posterior cingulate activation in mild cognitive impairment. *Neuroimage* **29**, 485-492.

[43] Celone KA, Calhoun VD, Dickerson BC, Atri A, Chua EF, Miller SL, DePeau K, Rentz DM, Selkoe DJ, Blacker D, Albert MS, Sperling RA (2006) Alterations in memory networks in mild cognitive impairment and Alzheimer's disease: an independent component analysis. *J Neurosci* **26**, 10222-10231.

[44] Klunk WE, Engler H, Nordberg A, Wang Y, Blomqvist G, Holt DP, Bergstrom M, Savitcheva I, Huang GF, Estrada S, Ausen B, Debnath ML, Barletta J, Price JC, Sandell J, Lopresti BJ, Wall A, Koivisto P, Antoni G, Mathis CA, Langstrom B (2004) Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Ann Neurol* **55**, 306-319.

[45] Kemppainen NM, Aalto S, Wilson IA, Nagren K, Helin S, Bruck A, Oikonen V, Kailajarvi M, Scheinin M, Viitanen M, Parkkola R, Rinne JO (2007) PET amyloid ligand [11C]PIB uptake is increased in mild cognitive impairment. *Neurology* **68**, 1603-1606.

[46] Gould RL, Brown RG, Owen AM, Bullmore ET, Williams SC, Howard RJ (2005) Functional neuroanatomy of successful paired associate learning in Alzheimer's disease. *Am J Psychiatry* **162**, 2049-2060.

[47] Perri R, Carlesimo GA, Serra L, Caltagirone C (2005) Characterization of memory profile in subjects with amnestic mild cognitive impairment. *J Clin Exp Neuropsychol* **27**, 1033-1055.

[48] Gronholm-Nyman P, Rinne JO, Laine M (2010) Learning and forgetting new names and objects in MCI and AD. *Neuropsychologia* **48**, 1079-1088.

[49] Seelye AM, Howieson DB, Wild KV, Moore MM, Kaye JA (2009) Wechsler Memory Scale-III Faces test performance in patients with mild cognitive impairment and mild Alzheimer's disease. *J Clin Exp Neuropsychol* **31**, 682-688.

[50] Dudas RB, Clague F, Thompson SA, Graham KS, Hodges JR (2005) Episodic and semantic memory in mild cognitive impairment. *Neuropsychologia* **43**, 1266-1276.

[51] Wagner AD, Shannon BJ, Kahn I, Buckner RL (2005) Parietal lobe contributions to episodic memory retrieval. *Trends Cogn Sci* **9**, 445-453.

[52] Rugg MD, Wilding EL (2000) Retrieval processing and episodic memory. *Trends Cogn Sci* **4**, 108-115.

[53] Velanova K, Jacoby LL, Wheeler ME, McAvoy MP, Petersen SE, Buckner RL (2003) Functional-anatomic correlates of sustained and transient processing components engaged during controlled retrieval. *J Neurosci* **23**, 8460-8470.

[54] Buckner RL, Wheeler ME (2001) The cognitive neuroscience of remembering. *Nat Rev Neurosci* **2**, 624-634.

Table 1.

Demographic variables and scores (SD) on the neuropsychological tasks for the groups

	Healthy controls	MCI higher-cognition	MCI lower-cognition
	n = 14	n = 13	n = 13
Gender	8F/6M	8F/5M	7F/6M
Age	67.21 (6.80)	68.62 (10.30)	67.08 (6.29)
Education	14.57 (3.76)	15.31 (3.83)	13.62 (3.91)
MDRS	140.33 (2.65)	139.31 (2.81)	129.92 (4.48)[b]
MMSE	29.29 (1.14)	28.85 (1.57)	26.46 (1.56)[b]
SMAF		-0.83 (0.83)	-1.33 (1.13)
Boston Naming Test		13.92 (1.12)	12.46 (1.71)[c]
Coding (WAIS-III)	11.29 (2.30)	9.77 (2.65)	8.92 (2.69)
Benton Judgment of line orientation		24.85 (3.58)	22.62 (4.11)
Copy of Rey's Figure (time)		216.69 (105.64)	251.38 (144.08)
Copy of Rey's Figure (score)		31.35 (3.26)	30.08 (3.48)
Immediate recall of Rey's Figure (score)		12.46 (5.19)	8.27 (5.99)
Delayed recall of Rey's Figure (score)		13.81 (4.99)	7.34 (5.21)[d]
Stroop 3rd plate (time)		29.68 (6.78)	32.57 (8.56)
Stroop 3rd plate (errors)		0.92 (1.04)	1.54 (2.54)
RL/RI-16 3rd free recall	12.21 (2.32)	10.15 (2.54)	5.23 (2.59)[b,e]
RL/RI-16 delayed free recall	12.71 (2.40)	9.52 (3.86)[a]	4.85 (3.08)[b,e]

[a] impairment relative to controls at $p < .05$; [b] impairment relative to controls at $p < .001$; [c] impairment relative to MCI higher-cognition at $p < .05$; [d] impairment relative to MCI higher-cognition at $p < .01$; [e] impairment relative to MCI higher-cognition at $p < .001$

Table 2.

Clusters (> 10 voxels) significantly more activated during the recognition of old/new word pairs condition than during the visual fixation condition for Healthy controls, MCI higher-cognition, and MCI lower-cognition, with cluster size, peak voxel MNI coordinates, and corresponding t-values.

Activated areas (Brodmann area) ($p < .05$, corrected)	Cluster size	x	y	z	t-value
Healthy controls: Recognition old/new > visual fixation					
Left occipital lobe (17, 18, 19)	193	-30	-75	-18	10.01
Right occipital lobe (17, 18)	117	15	-87	-3	8.63
Left inferior and superior parietal lobules and precuneus (7, 39, 40)	49	-30	-66	39	6.87
Right medial prefrontal cortex and anterior cingulate cortex (8, 32)	45	6	15	51	6.77
Right cerebellum	59	21	-54	-21	6.36
Left prefrontal cortex (44, 46)	15	-45	18	30	5.49
MCI higher-cognition: Recognition old/new > visual fixation					
Left occipital lobe (18, 19)	128	-30	-75	-18	10.58
Left/Right medial prefrontal cortex and anterior cingulate cortex (8, 32)	90	6	21	42	8.28
Left inferior and superior parietal lobules and precuneus (7, 39)	90	-27	-63	42	7.66
Right inferior and superior parietal lobules and precuneus (7, 39, 40)	81	33	-66	45	7.19
Right dorsolateral prefrontal cortex (46)	42	45	27	27	7.15

Right occipital lobe (17)	43	18	-90	-3	6.84
Right prefrontal cortex (6, 44, 45, 47)	33	33	27	0	6.69
Left prefrontal cortex (6, 44, 45, 47)	47	-39	0	33	5.98
Left precentral and postcentral gyri (3, 4)	17	-36	-30	54	5.71
MCI lower-cognition: Recognition old/new > visual fixation					
Left occipital lobe (17, 18, 19)	314	-18	-90	-9	10.14
Right occipital lobe (17, 18)	153	18	-90	-6	9.42
Left/Right superior/medial prefrontal cortex and anterior cingulate cortex (6, 8, 24, 32)	252	6	24	42	8.55
Left precentral and postcentral gyri and left inferior parietal lobule (2, 3, 4, 39, 40)	179	-36	-60	39	7.10
Left dorsolateral prefrontal cortex (46)	35	-42	24	27	7.02
Left prefrontal cortex (6, 44, 45)	70	-45	6	36	6.91
Right cerebellum	59	21	-54	-21	6.69
Right inferior parietal lobule (39, 40)	36	33	-63	36	6.44
Left ventrolateral prefrontal cortex (47)	21	-33	24	0	5.99
Right cerebellum	10	3	-63	-21	5.73
Right ventrolateral prefrontal (44, 45, 47)	17	36	24	3	5.65

Table 3.

Clusters (> 10 voxels) significantly more activated during the encoding of intact/rearranged word pairs condition than during the visual fixation condition for Healthy controls, MCI higher-cognition, and MCI lower-cognition, with cluster size, peak voxel MNI coordinates, and corresponding t-values.

Activated areas (Brodmann area) ($p < .05$, corrected)	Cluster size	x	y	z	t-value
Healthy controls: Recognition intact/rearranged > visual fixation					
Left occipital lobe (18, 19), left cerebellum	87	-30	-75	-18	8.13
Left/Right medial prefrontal cortex and anterior cingulate cortex (8, 32)	84	6	15	48	7.30
Left prefrontal cortex (6, 44)	18	-45	0	36	6.49
Left inferior and superior parietal lobules and precuneus (7, 39)	19	-30	-66	39	6.11
MCI higher-cognition: Recognition intact/rearranged > visual fixation					
Left inferior and superior parietal lobules and precuneus (7, 39, 40)	215	-27	-63	45	8.27
Right inferior and superior parietal lobules and precuneus (7, 39, 40)	133	33	-66	42	7.76
Left occipital lobe (17, 18, 19)	96	-27	-75	-15	7.68
Right occipital lobe (17, 18)	68	18	-90	-3	7.39
Left prefrontal cortex (6, 9, 44)	73	-42	12	33	7.32
Right medial prefrontal & premotor area and anterior cingulate cortex (6, 8, 32)	44	6	21	42	7.01
Right dorsolateral prefrontal cortex (9, 46)	39	48	15	27	6.78

Left dorsolateral prefrontal cortex (46)	11	-45	27	24	6.48
Right ventrolateral prefrontal (44, 45, 47)	20	33	27	-3	6.26
Right cerebellum	22	21	-54	-21	6.18
Left precentral and postcentral gyri and premotor area (3, 4, 6)	59	-39	-15	54	6.11
Left ventrolateral prefrontal cortex (45, 47)	17	-30	21	6	5.95
Right occipital lobe (19)	13	39	-66	-21	5.81
Right dorsolateral prefrontal cortex (46)	20	42	30	12	5.73
MCI lower-cognition: Recognition intact/rearranged > visual fixation					
Left occipital lobe (18)	56	-15	-87	-9	6.84
Right medial prefrontal cortex and anterior cingulate cortex (8, 32)	31	6	30	39	6.17
Right occipital lobe (17)	15	15	-87	-6	5.90

Table 4.

Clusters (> 5 voxels) significantly more activated in Healthy controls than in MCI higher- and MCI lower-cognition or significantly more activated in MCI higher- and MCI lower-cognition than in Healthy controls, with cluster size, peak voxel MNI coordinates, and corresponding t-values.

Activated areas (Brodmann area) ($p < .001$, uncorrected)	Cluster size	x	y	z	t-value
MCI higher-cognition > Healthy controls: Recognition intact/rearranged					
Right dorsolateral prefrontal cortex (9)	19	3	42	48	4.21
Left inferior parietal lobule (40)	12	-48	-45	48	3.90
Right lateral temporal lobe (37)	13	51	-57	-3	3.74
Right lateral temporal lobe (41)	6	42	-21	12	3.74
Left dorsolateral prefrontal cortex (9)	6	-45	15	42	3.61
Right ventrolateral prefrontal cortex (44)	6	48	12	24	3.58
Healthy controls > MCI higher-cognition: Recognition intact/rearranged					
None					
MCI higher-cognition > Healthy controls: Recognition old/new					
None					
Healthy controls > MCI higher-cognition: Recognition old/new					
Right cingulate & parahippocampal gyrus	25	6	-42	3	4.09
MCI lower-cognition > Healthy controls: Recognition intact/rearranged					
None					
Healthy controls > MCI lower-cognition: Recognition intact/rearranged					
None					

MCI lower-cognition > Healthy controls: Recognition old/new

Left dorsolateral prefrontal cortex (46)	22	-27	48	21	4.25
Left/Right medial prefrontal cortex (8)	20	0	36	51	4.10
Left inferior parietal lobule (40)	6	-48	-51	39	3.52
Left/Right anterior cingulate (24, 32)	8	6	33	6	3.51

Healthy controls > MCI higher-cognition: Recognition old/new

None

MCI higher-cognition > MCI lower-cognition: Recognition intact/rearranged

Right precuneus, superior parietal lobule(7)	28	24	-69	51	3.77
Left precuneus, superior parietal lobule (7)	12	-24	-66	51	3.71

MCI lower-cognition > MCI higher-cognition: Recognition intact/rearranged

None

MCI higher-cognition > MCI lower-cognition: Recognition old/new

None

MCI lower-cognition > MCI higher-cognition: Recognition old/new

None

Table 5.

Clusters (> 10 voxels) significantly more activated during the recognition of old/new word pairs condition than during the recognition intact/rearranged word pairs or during the recognition of intact/rearranged word pairs condition than during the recognition old/new word pairs for Healthy controls, with cluster size, peak voxel MNI coordinates, and corresponding t-values.

Activated areas (Brodmann area) ($p < .005$, uncorrected)	Cluster size	x	y	z	t-value
Healthy controls: Recognition old/new > Recognition intact/rearranged					
Left/Right medial prefrontal cortex (10)	26	-3	66	3	3.30
Left parahippocampal gyrus	7	-12	-39	3	3.18
Right parahippocampal gyrus	9	24	-30	-15	3.17
Right middle/superior temporal gyrus (19, 39)	10	48	-63	15	2.99
Healthy controls: Recognition intact/rearranged > Recognition old/new					
Left basal ganglia	21	-6	3	-3	3.37
Right anterior cingulated cortex (24)	11	6	36	3	2.96

Figure Captions

Figure 1. Progression of theoretical brain activation for item recognition and associative recognition in normal individuals and patients with milder mild cognitive impairment (MCI), more severe MCI, and Alzheimer's disease (AD).

Figure 2. Scores obtained on the recognition of old/new word pairs condition and on the recognition of intact/rearranged word pairs condition by the Healthy controls, MCI higher-cognition, and MCI lower-cognition groups.

Figure 3. Cerebral activations ($p < .05$, FWE corrected, cluster size > 5 voxels) on the recognition of old/new word pairs condition and on the recognition of intact/rearranged word pairs condition by the Healthy controls, MCI higher-cognition, and MCI lower-cognition groups.

Figure 4. Group differences in cerebral activations ($p < .001$, uncorrected, cluster size > 5 voxels) for (a) areas showing significantly more activation in the MCI higher-cognition group than in Healthy controls for the recognition intact/rearranged task and (b) areas showing significantly more activation in the MCI lower-cognition group than in Healthy controls for the recognition old/new task.

Figure 1. Progression of theoretical brain activation for item recognition and associative recognition in normal individuals and patients with milder MCI, more severe MCI, and Alzheimer's disease (AD).

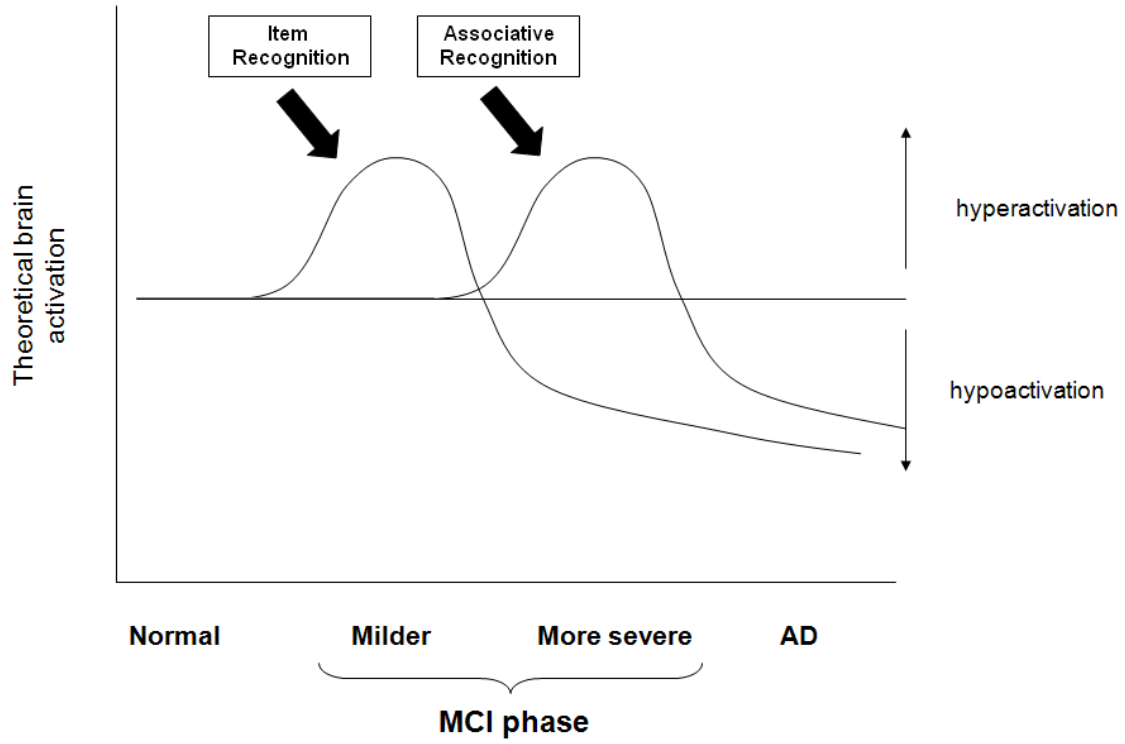


Figure 2. Scores obtained on the recognition of old/new word pairs condition and on the recognition of intact/rearranged word pairs condition by the Healthy controls, MCI higher-cognition, and MCI lower-cognition groups.

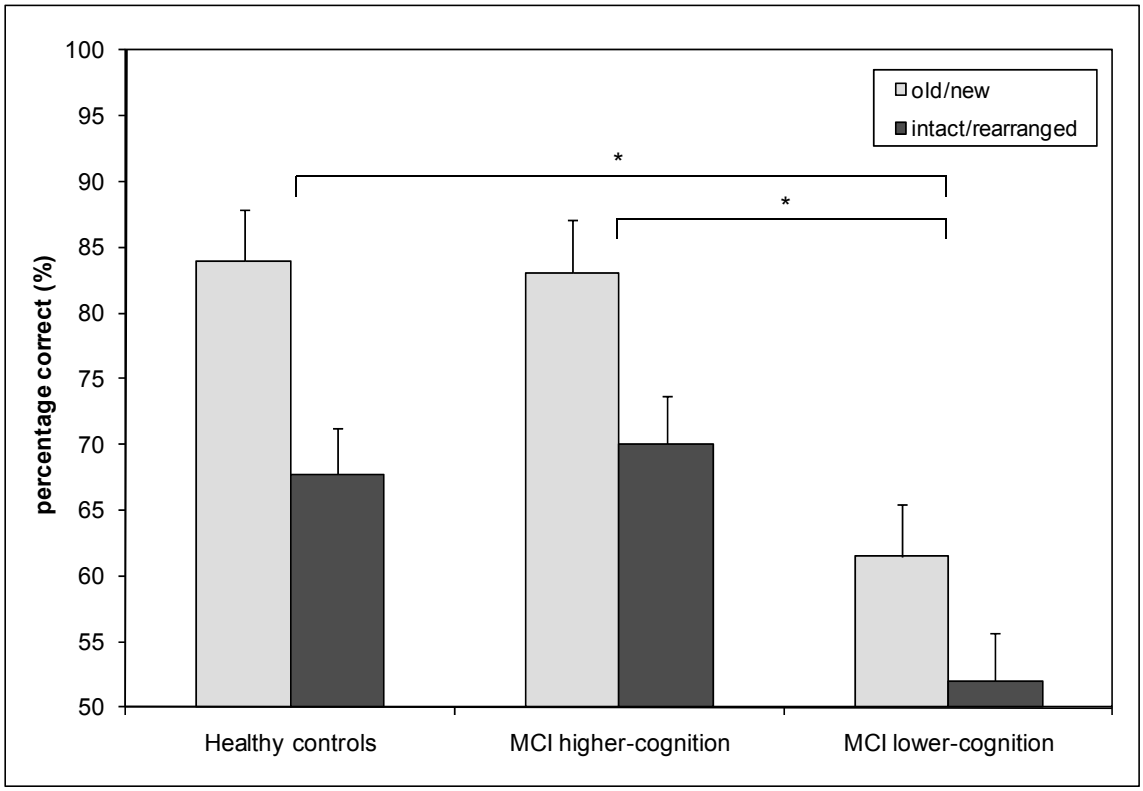


Figure 3. Cerebral activations ($p < .05$, FWE corrected, cluster size > 5 voxels) on the recognition of old/new word pairs condition and on the recognition of intact/rearranged word pairs condition by the Healthy controls, MCI higher-cognition, and MCI lower-cognition groups.

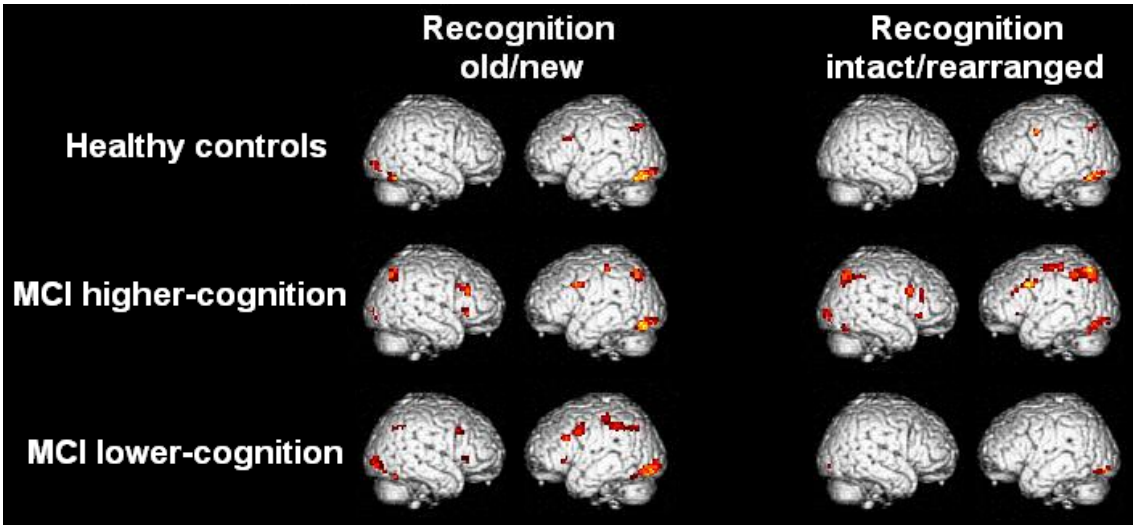
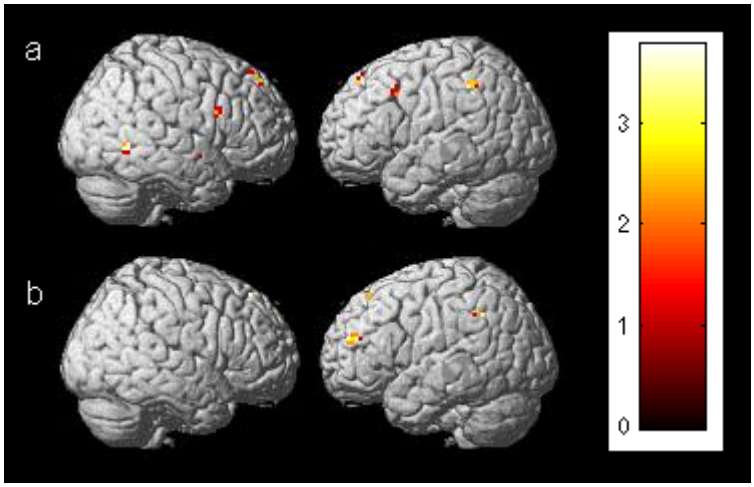


Figure 4. Group differences in cerebral activations ($p < .001$, uncorrected, cluster size > 5 voxels) for (a) areas showing significantly more activation in MCI higher-cognition than Healthy controls for the recognition intact/rearranged task and (b) areas showing significantly more activation in MCI lower-cognition than Healthy controls for the recognition old/new task.



CHAPITRE 6

Article n° 5

Emergence and breakdown of neural plasticity during mild cognitive impairment

Francis Clément, Sylvie Belleville & Serge Gauthier

Cortex (en révision)

Abstract

Our goal was to test the effect of disease severity on the brain activation associated with two executive processes: manipulation and divided attention. This was achieved by administrating a manipulation task and a divided attention task using functional magnetic resonance imaging to 24 individuals with mild cognitive impairment and 14 healthy controls matched for age, sex and education. The Mattis Dementia Rating Scale was used to divide persons with mild cognitive impairment into those with better and worse cognitive performances. Both tasks were associated with more brain activation in the mild cognitive impairment group with higher cognition than in healthy controls, particularly in the left frontal areas. Correlational analyses indicated that greater activation in a frontostriatal network hyperactivated by the higher-cognition group was related with better task performance, suggesting that these activations may support functional reorganization of a compensatory nature. By contrast, the lower-cognition group failed to show greater cerebral hyperactivation than controls during the divided attention task and showed less brain activation than controls in the left ventrolateral cortex, a region commonly hypoactivated in patients with Alzheimer's disease, during the manipulation task. These findings indicate that, during the early phase of mild cognitive impairment, executive functioning benefits from neural reorganization, but that a breakdown of this brain plasticity characterizes the late stages of the disease.

The last decade has seen considerable interest in the study of the cognitive and neural changes experienced by individuals with mild cognitive impairment (MCI) (Petersen et al., 1999; Petersen et al., 2001), a population at high risk of developing Alzheimer's disease (AD) (Gauthier et al., 2006). While memory has been the main topic of interest, more attention is now being given to non-memory deficits, particularly those that affect executive functioning (Dannhauser et al., 2005; Belleville et al., 2007; Belanger and Belleville, 2009). Such investigations are clinically relevant because executive deficits have been shown to exacerbate memory deficits (Ranganath et al., 2005) and could represent a critical factor in the progression from MCI to dementia (Royall et al., 2005). Therefore, the first goal of this study was to contribute to a better understanding of the brain changes that underlie executive decline in MCI.

Our second goal was to investigate whether those changes could be modulated by mechanisms of brain compensation and plasticity. It has been proposed that there is a functional trade-off between brain damage and compensatory mechanisms over the course of AD: When the disease is mild, the brain might be able to compensate for the effect of the lesions by recruiting additional functional networks that include the lesioned region and/or distal areas, but, as lesions accumulate, the neural system might gradually lose this compensatory ability (Friston and Price, 2003; Prvulovic et al., 2005). In this view, individuals with MCI are expected to be able to reorganize their functional networks in response to the brain damage because they are in a very early phase of the disease. As they acquire more neuropathologies, however, a breakdown of this functional reorganization should be observed. Yet, despite its important implications, this model has been tested in only a few studies (Celone et al., 2006; Clement and Belleville, 2010;

Clement et al., 2010), and none have investigated whether it characterizes executive functions.

This study measured the brain activation patterns of individuals with MCI by using tasks that involve two executive processes, manipulation and divided attention. The effect of disease severity was also measured by dividing MCI individuals into those with lower and higher cognitive functioning. We hypothesized that MCI participants with higher cognition would show increased brain activation compared with healthy controls (i.e., hyperactivation) and that these hyperactivations would be positively correlated with task performances. By contrast, MCI participants with lower cognition should show no evidence of hyperactivation and exhibit less activation than controls. Moreover, these hyper/hypoactivations should be observed in regions altered in AD and/or involved in executive functioning (i.e. lateral prefrontal cortex, precuneus and posterior parietal areas, Collette et al., 1999; Wager and Smith, 2003; Johnson and Zatorre, 2006). Findings in accordance with these hypotheses would provide empirical evidence of the presence of neural reorganization during the early stages of MCI and of a breakdown of this mechanism during the later stages of the disease.

Method

Participants

Thirty-eight participants, 14 healthy older adults and 24 persons with MCI, took part in this study. French was the first language of all participants, and all tasks were conducted in French. Sociodemographic characteristics of the two groups are shown in Table 1.

Participants with MCI were referred from memory clinics and met the following four criteria (Petersen et al., 1999; Petersen et al., 2001; Winblad et al., 2004) for amnestic single or multiple domain MCI: (1) memory complaint corroborated by an informant when possible; (2) performance at least 1.5 standard deviations (SD) below the average level of persons of similar age and education on at least one memory test from the neuropsychological battery (amnestic single domain MCI subtype) or on at least one memory test plus one or more tests measuring other cognitive domains (amnestic multiple domain MCI subtype); (3) neither global cognitive impairment on the basis of the Mini-Mental State Examination (MMSE) (using a cutoff for age and education) nor a significant impact on daily functions as measured by the SMAF functional impairment scale (Desrosiers et al., 1995) and clinical interview with an informant; and (4) absence of dementia based on clinical criteria (American Psychiatric Association, 2000). Individuals with MCI completed an extensive neuropsychological evaluation that covered episodic memory (free and cued word recall task: Rappel Libre/Rappel Indicé-16; Van der Linden et al., 2004; text memory of the *Batterie d'Efficience Mnésique*, BEM; Signoret, 1991; recall of Rey Complex Figure, Rey, 1959), executive functions (third plate of Stroop-Victoria, Regard, 1981; and copy of Rey Complex Figure, Rey, 1959), visuospatial processing (Benton Judgment of line orientation, Benton et al., 1983), speed of information processing (Coding of the WAIS-III, Wechsler, 1997), language (Boston Naming Test, Kaplan et al., 1983) and global cognitive functions (Mattis Dementia Rating Scale, MDRS, Mattis, 1976; MMSE, Folstein et al., 1975). Individuals with MCI also underwent an extensive medical, neurological and neuroradiological examination prior to enrolment in the study to exclude the presence of any other

significant systemic, neurological or psychiatric condition that could explain their cognitive difficulties.

Participants with MCI were separated into two groups using a split-median of their scores on the MDRS. The MDRS was preferred over the MMSE for identifying disease severity levels in MCI participants because it covers a broader range of cognitive functions and has more variability, and because MCI participants do not show a ceiling effect on this scale. The split-median identified 12 persons with a higher level of overall cognitive functioning (MCI higher-cognition) and 12 persons with a lower level of overall cognitive functioning (MCI lower-cognition).

Two years after participating in this study, the MCI participants underwent the same medical, neurological, neuroradiological and neuropsychological evaluations to determine whether they had developed AD or showed significant cognitive decline. Alzheimer's disease was diagnosed by the referring clinicians using the NINCDS-ADRDA (McKhann et al., 1984) and DSM-IV criteria. Cognitive decline was defined as a reduced performance by more than 1 SD on at least two neuropsychological tests (Belleville et al., 2007). The determination of cognitive decline or progression to AD was performed blind to the group membership identified here. At follow-up, 67% of the MCI higher-cognition participants were found to have remained stable, 33% showed a cognitive decline, and none had developed AD. Among the MCI lower-cognition participants, 33% were found to have remained stable, 8% showed cognitive decline, and 58% had developed AD. Chi-square analyses indicated a higher proportion of conversion

to AD in the MCI lower-cognition group ($\chi^2 = 2.66$, $p < .05$) than in the MCI higher-cognition group.

Healthy older adults were recruited from the community and, to ensure they did not suffer from any cognitive deficits, were subjected to a clinical and neuropsychological evaluation involving the assessment of global cognitive functions (MDRS,[4] Mattis, 1976; MMSE, Folstein et al., 1975; Montreal Cognitive Assessment, MOCA; Nasreddine et al., 2005), speed of information processing (Coding subtest of the WAIS-III; Wechsler, 1997) and episodic memory (cued and free word recall task: RL/RI-16, Buschke, 1984; Van der Linden et al., 2004).

The study was approved by the *Comité mixte d'éthique de la recherche du Regroupement Neuroimagerie/Québec* (CMER-RNQ).

Stimuli and procedure

Manipulation task: Manipulation was measured by having participants complete equations that require on-line processing and manipulation of the alphabet (Logan, 1988; Compton and Logan, 1991). Alphanumeric problems took the form of the equation $x \pm 1 = y$, where x was a letter of the alphabet chosen randomly between A and L followed by a plus (+) or minus (–) sign and the number 1, and where y was a proposed solution to the problem. Half of the equations were true (e.g., A + 1 = B), and the other half were false (e.g., A + 1 = C). Half of the equations used a plus sign, and the other half used a minus sign (e.g., G – 1 = F). The proposed solution was either 1 letter (50% of

[4] Five healthy controls did not complete the MDRS, but did complete the MMSE and MOCA.

trials) or 2-3 (50% of trials) letters away from the solution. Equations were visually presented and remained on the screen for 5 s. Participants were asked to determine whether the solution to the equation was correct and to answer by pressing one key with their right middle finger for true equations and another key with their right ring finger for false equations. After the training session (see below), no feedback was given.

Divided attention task: Divided attention was measured by having participants combine the alphanumeric equation task with a simple visual detection task. A new set of alphanumeric equations was created for the divided attention task, with the same constraints as in the manipulation task. Participants were asked to judge the accuracy of alphanumeric equations that were first presented in black print but changed to red unexpectedly during the trial. Participants were asked to pay attention to this colour change while completing the equation and report the change when it occurred. Participants judged the accuracy of the equation by pressing one key with their right middle finger for true equations and another key with their right ring finger for false equations, and reported the colour change by pressing a third key with their right index finger. Participants were asked to give equal priority to both tasks and to answer as quickly and accurately as possible. Each equation was presented individually and remained on the screen for 5 s. No feedback was given during the task. An instruction screen appeared for 4 s at the beginning of each block to remind the subject of the instructions. Correct responses were recorded.

Control condition: The control condition for both the manipulation and the divided attention tasks involved the visual presentation of series of random characters.

Each series was composed of two random letters (from A to L), two random numbers (from 1 to 9), one plus or minus sign, and one equal sign—all placed in random positions (e.g., = F 3 H + or 4 – = B L), with 37.5% of the strings presented in red and 62.5% in white. Participants were asked to press a key with their right index finger each time the random string of letters, numbers, and signs was red. Each string was presented individually and remained on the screen for 2.5 s.

Procedure specific to functional magnetic resonance imaging

The tasks were programmed with E-prime, and stimuli were visually presented and mirror-projected. Subjects with corrected vision wore goggles appropriate for magnetic resonance imaging (MRI). The procedure consisted of one run composed of five series of visual fixation (14 s), manipulation task (44 s), control task (44 s), visual fixation (14 s) and divided attention (44 s). The visual fixation block consisted of fixation on crosshairs.

Participants were first trained on the functional MRI (fMRI) procedure and practised in a simulator that mimics the fMRI environment (in terms of task, body position, sound, etc.) one week prior to scanning. For this practice session, participants completed 10 trials in each condition. To limit repetition effects, the stimuli used for the practice session were different than those used for the actual fMRI task (i.e., letters M through Z for the practice and A through L for the fMRI task).

Data acquisition

Magnetic resonance imaging was performed using a SIEMENS 3T Magnetom TRIO System (Erlangen, Germany) at the Unité de Neuroimagerie Fonctionnelle (UNF) of *Institut universitaire de gériatrie de Montréal*. Functional MR images were acquired using gradient-echo echo-planar imaging sequences (GE-EPI) sensitive to blood oxygen level-dependent (BOLD) contrast (TR/TE = 2000/30 ms, flip angle = 90 °; 31 interleaved slices, voxel size = 3.75×3.75×5 mm^3 with a gap of 1 mm, field of view = 240 mm, matrix = 64×64). A three-dimensional (3D) structural image was taken at the end of the session and consisted of a sagittal T1-weighted 3D-MPRAGE sequence (TR/TE = 1950/3.93 ms, flip angle = 15 °; 176 slices, voxel size = 1×1×1 mm^3, field of view = 256 mm, matrix = 256×256).

Image processing and data analysis

Data were analyzed in MATLAB 7.0 (http://www.mathworks.com) using the statistical parametric mapping software SPM5 (http://www.fil.ion.ucl.ac.uk/spm/). The first three volumes were automatically discarded by the fMRI scanner in order to allow the magnetization to reach equilibrium. Functional images were first converted into Analyze format and unwarped. They were then realigned to the first volume acquired in the session, and a mean realigned volume was created for each subject. All the realigned volumes from each subject were spatially normalized into the Montreal Neurological Institute (MNI) stereotactic space and spatially smoothed with an 8-mm Gaussian kernel. Low-frequency noise was removed with a high-pass filter of 208 s. The instruction blocks were modelled as a condition of no-interest. In the first level analysis, the coefficients for each contrast were estimated separately in fixed effect models for each

participant. A random effects (RFX) analysis was then performed by calculating a two-way analysis of variance (ANOVA) with Group (healthy older adults, MCI higher-cognition, MCI lower-cognition) as a between-subject factor and Condition (manipulation, divided attention, control) as a within-subject factor, with non-sphericity corrections, replications over subjects and correlated repeated measures. Manipulation task activations were calculated with the contrast (manipulation > control task). Divided attention task activations were calculated by conducting an interaction analysis between the contrasts (divided attention > manipulation) and (control task > visual fixation). This method of cognitive subtraction has been shown to be an appropriate method for measuring areas that show greater activation in a dual task than in the single tasks alone (Szameitat et al., 2002). Two criteria were used to define significant regions for the between-group analyses: (1) a voxel-level threshold of $p < .001$ uncorrected and (2) a cluster-level threshold of $p < .05$. As mentioned in the results section, all neuroimaging analyses were performed with the performance scores of each subject as a covariate.

Results

Sociodemographic and clinical data

Sociodemographic neuropsychological data are shown in Table 1. They were analyzed with one-way ANOVAs using Group (healthy controls, MCI higher-cognition, MCI lower-cognition) as a between-subject factor. Tukey's post hoc tests were used to determine the source of the effect when significant. The groups did not differ in age, $F(2,35) = 0.09$, N.S., or education, $F(2,37) = 0.13$, N.S. As expected, both MCI subgroups showed lower episodic memory performances than healthy controls, and MCI

lower-cognition showed lower episodic memory abilities than MCI higher-cognition. In addition, the MCI lower-cognition group scored lower than the other two groups on a task that reflects speed and executive functioning (i.e., Coding). Moreover, chi-square analyses indicated a similar male-to-female ratio in the three groups ($\chi^2 < 0.01$, in all cases N.S.).

Examination of individuals' clinical profiles revealed that, within the MCI higher-cognition group, six persons met criteria for the amnestic single domain subtype and six met criteria for amnestic multiple domain MCI. Within the MCI lower-cognition group, four persons met criteria for the amnestic single domain subtype and eight met criteria for amnestic multiple domain MCI. A chi-square analysis indicated that the proportion of persons with single and multiple domain MCI was equivalent in the two groups ($\chi^2 = 0.69$, N.S.).

Cognitive data

For the manipulation task, performances were calculated as the mean percentage of correctly solved equations. A one-way ANOVA with Group (healthy controls, MCI higher-cognition, MCI lower-cognition) as a between-subject factor was performed and indicated a significant Group effect, $F(2,35) = 5.30$, $p = .01$. Tukey's post hoc test revealed that both MCI groups had a lower performance on the manipulation task compared with healthy controls, $p < .05$ and $p < .01$ for MCI higher-cognition and MCI lower-cognition, respectively. The performances of the two MCI groups were not significantly different (Figure 1).

For the divided attention task, we used the mean percentage of correctly solved equations and the mean percentage of correctly detected red targets as dependent variables. Separate two-way ANOVAs with Group (healthy controls, MCI higher-cognition, MCI lower-cognition) as a between-subject factor and Condition (focused attention, divided attention) as a within-subject factor were computed for each dependent variable. For the equation problems, a Group effect, $F(2,35) = 8.46$, $p < .001$, and a Condition effect, $F(1, 35) = 217.79$, $p < .001$, were observed, but no interactions were noted. Unsurprisingly, the Condition effect showed that participants performed better with focused than with divided attention. Tukey's post hoc test revealed that the Group effect was due to worse performance of both MCI higher-cognition and MCI lower-cognition compared with healthy controls, $p < .05$. Only a Condition effect was found in the detection task, $F(1,35) = 99.22$, $p < .001$, with participants performing better when they completed the task with focused rather than divided attention.

Divided attention cost scores were then calculated for each dependent variable with the following formula:

$$[(\text{focused} - \text{divided}) / \text{focused}] \times 100\%.$$

Two separate one-way ANOVAs with Group (healthy controls, MCI higher-cognition, MCI lower-cognition) as a between-subject factor were computed on the divided attention cost scores for equations and for detection. A Group effect was observed on the equations cost score, $F(2,35) = 4.51$, $p < .05$. Tukey's post hoc tests revealed that MCI lower-cognition had a greater divided attention cost score than healthy controls for equations, $p < .05$, but that MCI higher-cognition did not differ from healthy controls (Figure 2). No Group effect was observed for the divided attention cost scores

for detection, F(2,35) = 1.53, N.S. (Figure 2). Because group differences in performance were observed on some of the tasks, all the following neuroimaging analyses were performed with the performance scores of each subject as a covariate.

Brain imaging data: Within-group comparisons

Manipulation. All three groups showed activation in the medial frontal gyri and the anterior cingulate gyrus (BA 6, 8, 32), both bilaterally, as well as in the right cerebellum (Table 2). The MCI lower-cognition group showed no additional activations. Healthy controls showed activations in the left inferior frontal gyrus (BA 44, 45, 46), the right inferior frontal gyrus (BA 45, 47), the left middle frontal gyrus (BA 9), the precuneus bilaterally (BA 7), the left premotor area (BA 6), the occipitoparietal areas bilaterally (BA 7, 19, 39, 40) and the left cerebellum, whereas MCI higher-cognition showed additional activations in the left inferior frontal gyrus (BA 44, 45, 47) and the left superior frontal gyrus (BA 8).

Divided attention. As displayed in Table 3, all three groups showed bilateral activation of the medial precuneus and dorsal posterior cingulate gyrus (BA 7, 31). The MCI lower-cognition group showed additional activations in the temporoparietal areas (BA 39 bilaterally and BA 22 on the left side) and in the right precuneus (BA 7). The MCI higher-cognition group showed additional activations in a frontostriatal network on the left side (BA 47, caudate, putamen), the right superior frontal gyrus (BA 6), the anterior cingulate cortex bilaterally (BA 24, 32), the right paracentral lobule (BA 5), the left middle temporal gyrus (BA 21), the right entorhinal and perirhinal areas (BA 28, 35), the left occipitotemporal areas (BA 36, 37), the right inferior parietal lobule and

supramarginal and angular gyri (BA 39, 40), the right posterior cingulate cortex (BA 31) and the left cerebellum.

Brain imaging data: Between-group comparisons

Manipulation. When the activations were compared statistically across groups, MCI higher-cognition showed increased activation compared with healthy controls in the left postcentral gyrus (BA 43) and the left middle and superior frontal gyri (BA 6, 8) (see Table 4), but less activation in the left cerebellum. By contrast, MCI lower-cognition showed only hypoactivation, which was found in the left inferior and middle frontal gyri (BA 45, 46) and the left occipitotemporal areas (BA 19, 37). There were no areas showing hyperactivation in the MCI lower-cognition group.

Divided attention. As displayed in Table 5, MCI higher-cognition showed significantly increased activation compared with healthy controls in a large frontostriatal network that involves the left inferior frontal gyrus (BA 47), the left insula (BA 13), the left caudate and putamen, and the anterior cingulate cortex bilaterally. They also showed hyperactivation in the left fusiform gyrus (BA 36, 37), the left thalamus, and the left cerebellum and midbrain. There were no areas showing significant differences in activation when MCI lower-cognition were compared with healthy controls.

Correlations between activations and performances

Correlations were computed between task performance and the level of activation in the clusters that showed differences in activation between individuals with MCI and healthy controls (see Table 5). The average beta values of the regions of interest were extracted with MarsBaR (Brett et al., 2002) for each participant and condition. Pearson's

correlations were then performed in SPSS 13.0 (http://www.spss.com). The performance variables used for the correlations were the percentage of correctly solved equations in the manipulation task and the percentage of correctly solved equations and correctly detected targets in the divided attention task. As indicated in Table 5, significant correlations were found only in the MCI higher-cognition group. In this group, performance in the divided attention task was positively correlated with activation in a cluster comprising the right putamen, the anterior cingulate cortex, the left caudate, the left insula and the left inferior frontal gyrus. In this case, greater activation was associated with better divided attention performance.

Discussion

The goal of this study was to assess the brain activation patterns of individuals with MCI during tasks involving executive functions and to evaluate the effect of disease severity on those patterns. Two executive components were measured: brain activation associated with the manipulation of information and brain activation associated with divided attention. The effect of disease severity was determined by distinguishing patients on the basis of their scores on the MDRS, an index of global cognitive functioning. It was hypothesized that persons with MCI with better cognitive function (MCI higher-cognition) would show neural reorganization (as reflected by hyperactivation) during both tasks, whereas brain plasticity would fail in those with more severe MCI (MCI lower-cognition), as reflected by hypoactivation. Interestingly, our MCI higher-cognition and MCI lower-cognition subgroups showed a mean MMSE score very similar to those associated with the early MCI and late MCI subgroups of the Alzheimer's Disease Neuroimaging Initiative 2 (ADNI 2) project (Aisen et al., 2010). In

the following discussion, we first present the data for healthy controls in order to identify the networks that are typically required to execute the specific task. This information will then be used to shed light on whether the areas of change in MCI are those normally involved in each task.

Healthy controls

During manipulation, healthy older adults showed activations in several regions that are known to be involved in the manipulation of information in younger adults (Collette et al., 1999; D'Esposito et al., 1999; Smith and Jonides, 1999; Wager and Smith, 2003). These regions include the ventrolateral (BA 44, 45, 47) and dorsolateral (BA 9, 46) prefrontal cortex and the precuneus (BA 7), both bilaterally. In young adults, the division of attention across tasks has been associated with activity in either the left ventrolateral and dorsolateral prefrontal cortex or the posterior parietal areas (Bunge et al., 2000; Szameitat et al., 2002; Loose et al., 2003; Schubert and Szameitat, 2003; Johnson and Zatorre, 2006). The pattern of brain activation associated with divided attention in our group of healthy older adults is more consistent with the findings of posterior activations: divided attention was associated with activation in the precuneus as well as in a large cluster within the posterior parietal areas. The pattern found here is also consistent with the more widely distributed network of activation that has been reported in healthy older adults (Rajah and D'Esposito, 2005).

MCI higher-cognition

It was expected that persons in the MCI higher-cognition group still had sufficient neural resources to allow neural reorganization and that this would result in either

expanded areas of activation or increased activation when compared with controls (hyperactivation). This was indeed the case. During the manipulation task, the MCI higher-cognition group showed hyperactivations in the left middle and superior frontal gyri and the left postcentral gyrus. It must be noted that the left middle and superior frontal gyri were also activated in healthy older adults, though to a lesser degree, and have been shown to be activated during manipulation tasks (Collette et al., 1999; D'Esposito et al., 1999). By contrast, the left postcentral gyrus is not activated in healthy older adults. Thus, during manipulation, the MCI higher-cognition group showed increased activation in a combination of regions typically involved in the task and new regions.

Similarly, during the divided attention task, the MCI higher-cognition group showed hyperactivations in areas that were also activated by healthy controls (i.e., the putamen and the left prefrontal cortex). Interestingly, the left prefrontal cortex has been identified as a key region in a number of studies involving divided attention tasks (Bunge et al., 2000; Szameitat et al., 2002; Loose et al., 2003; Schubert and Szameitat, 2003; Johnson and Zatorre, 2006). However, MCI higher-cognition also showed activation in areas that were not activated by controls (e.g., the left fusiform gyrus and the left insula) and are not typically associated with divided attention.

Correlational analyses indicated that some of these activations were of a compensatory nature. In particular, a large frontostriatal area of hyperactivation was highly correlated with performance on the divided attention task ($r = 0.62$) in the MCI higher-cognition group. Because divided attention is unimpaired in this group, this

correlation suggests that this increased activation might partly support their maintenance of intact performance on this task and, hence, represent compensatory mechanisms. Furthermore, the involvement of the striatal regions in this correlation is interesting: While the basal ganglia have traditionally been involved in the control of movement, recent studies indicate that they might play a role in executive control (Monchi et al., 2006; Nagano-Saito et al., 2008), perhaps because different parts of the striatum project to regions within the dorsolateral prefrontal and lateral orbitofrontal cortices (Middleton and Strick, 1994, 2000).

MCI lower-cognition

The MCI lower-cognition group comprised individuals with MCI who showed the most severe cognitive impairment and were thus considered to be in a more advanced stage of the disease. As expected, participants in this group performed significantly worse on the divided attention task than those in MCI higher-cognition, which supports our contention that participants in this group were in a more severe stage of the disease. Our model proposes that these individuals should be characterized by reduced activation relative to controls. Again, our results generally support this hypothesis. During manipulation, MCI lower-cognition showed only areas of hypoactivation, which were found in the left inferior and middle frontal gyri (BA 45, 46), regions typically involved in the manipulation of information (Collette et al., 1999; D'Esposito et al., 1999; Wager and Smith, 2003), as well as in the left occipitotemporal areas (BA 19, 37). Therefore, it seems that the MCI lower-cognition group failed to recruit some of the crucial networks activated by healthy older adults during this task. In turn, this under-recruitment may be responsible for their poor performances on the task. Further, it is notable that the left

ventrolateral cortex was hypoactivated in the MCI lower-cognition group, a finding that has frequently been reported in patients with AD during similar tasks requiring executive functions (Yetkin et al., 2005; Lim et al., 2008). Finally, during the divided attention task, the MCI lower-cognition group showed no clusters that differed significantly from the level of activation in healthy controls, a finding that contrasts markedly with the hyperactivation characterizing the MCI higher-cognition group.

Limitations

Some limitations of the present study must be mentioned. Because we used a cross-sectional design rather than a longitudinal one, it is impossible to completely rule out the possibility that patients defined on the basis of their clinical severity belong to different subgroups rather than lie on different points of a severity continuum. Along the same line, and as there is no gold standard for indexing disease severity, biological markers such as whole brain volume or beta amyloid brain load could have been used instead of the MDRS. However, we favoured a clinical rather than a biological index because clinical measures are closer to the criteria on which the diagnoses of MCI and AD are established and because measures of brain activation may not be entirely independent of typical biological measures. Another limitation could be the use of a blocked fMRI design rather than an event-related design because blocked designs do not allow the distinction between correct and incorrect answers. However, they do offer maximal detection power (Liu, 2004) and are more manageable for patients with cognitive deficits, as the conditions alternate less frequently than in an event-related design.

Summary

We found that MCI individuals with milder cognitive symptoms show large areas of hyperactivation associated with executive functioning. This effect is not task specific, as it was found with both the manipulation and divided attention tasks, although the localization of the hyperactivations varies as a function of the cognitive process involved. Importantly, our data indicates that these areas of hyperactivation can support successful compensation, as a large performance-correlated frontostriatal circuit was found during the divided attention task. By contrast, individuals with MCI who exhibit more severe overall cognitive deficits experience a breakdown of this purported brain plasticity phenomenon: Not only do they not show hyperactivation during the divided attention task, but they also show evidence of hypoactivation during the manipulation task. This breakdown is accompanied by an impaired level of performance on both tasks. Thus, our findings suggest an early MCI phase characterized by increased activation and compensatory neural reorganization is followed by a breakdown of these mechanisms as the disease progresses. It is possible that this shift in brain activation and the breakdown of compensatory mechanisms signal the critical moment of brain deterioration and executive function deficit that occur just before these individuals progress to a stage in which they meet criteria for dementia.

References

Aisen PS, Petersen RC, Donohue MC, Gamst A, Raman R, Thomas RG, Walter S, Trojanowski JQ, Shaw LM, Beckett LA, Jack CR, Jr., Jagust W, Toga AW, Saykin AJ, Morris JC, Green RC, Weiner MW (2010) Clinical Core of the Alzheimer's Disease Neuroimaging Initiative: progress and plans. Alzheimers Dement 6:239-246.

American Psychiatric Association (2000) Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, 4th Edition: American Psychiatric Publishing, Inc.

Belanger S, Belleville S (2009) Semantic inhibition impairment in mild cognitive impairment: a distinctive feature of upcoming cognitive decline? Neuropsychology 23:592-606.

Belleville S, Chertkow H, Gauthier S (2007) Working memory and control of attention in persons with Alzheimer's disease and mild cognitive impairment. Neuropsychology 21:458-469.

Benton AL, Hamsher K, Varney NR, Spreen O (1983) Contributions to neuropsychological assessment. New York: Oxford University Press.

Brett M, Anton J-L, Valabregue R, Poline J-P (2002) Region of interest analysis using an SPM toolbox In: 8th International Conference on Functional Mapping of the Human Brain, June 2-6, 2002,. Sendai, Japan. Available on CD-ROM in NeuroImage, Vol 16, No 2.

Bunge SA, Klingberg T, Jacobsen RB, Gabrieli JD (2000) A resource model of the neural basis of executive working memory. Proc Natl Acad Sci U S A 97:3573-3578.

Buschke H (1984) Cued recall in amnesia. Journal of Clinical Neuropsychology 6:433-440.

Celone KA, Calhoun VD, Dickerson BC, Atri A, Chua EF, Miller SL, DePeau K, Rentz DM, Selkoe DJ, Blacker D, Albert MS, Sperling RA (2006) Alterations in memory networks in mild cognitive impairment and Alzheimer's disease: an independent component analysis. J Neurosci 26:10222-10231.

Clement F, Belleville S (2010) Compensation and disease severity on the memory-related activations in mild cognitive impairment. Biol Psychiatry 68:894-902.

Clement F, Belleville S, Mellah S (2010) Functional neuroanatomy of the encoding and retrieval processes of verbal episodic memory in MCI. Cortex 46:1005-1015.

Collette F, Salmon E, Van der Linden M, Chicherio C, Belleville S, Degueldre C, Delfiore G, Franck G (1999) Regional brain activity during tasks devoted to the central executive of working memory. Brain Res Cogn Brain Res 7:411-417.

Compton BJ, Logan GD (1991) The transition from algorithm to retrieval in memory-based theories of automaticity. Mem Cognit 19:151-158.

D'Esposito M, Postle BR, Ballard D, Lease J (1999) Maintenance versus manipulation of information held in working memory: an event-related fMRI study. Brain Cogn 41:66-86.

Dannhauser TM, Walker Z, Stevens T, Lee L, Seal M, Shergill SS (2005) The functional anatomy of divided attention in amnestic mild cognitive impairment. Brain 128:1418-1427.

Desrosiers J, Bravo G, Hebert R, Dubuc N (1995) Reliability of the revised functional autonomy measurement system (SMAF) for epidemiological research. Age Ageing 24:402-406.

Folstein MF, Folstein SE, McHugh PR (1975) Mini-Mental State: A practical method for grading the cognitive state of patients for the clinician. Journal of Psychiatric Research 12:189-198.

Friston KJ, Price CJ (2003) Degeneracy and redundancy in cognitive anatomy. Trends Cogn Sci 7:151-152.

Gauthier S, Reisberg B, Zaudig M, Petersen RC, Ritchie K, Broich K, Belleville S, Brodaty H, Bennett D, Chertkow H, Cummings JL, de Leon M, Feldman H, Ganguli M, Hampel H, Scheltens P, Tierney MC, Whitehouse P, Winblad B (2006) Mild cognitive impairment. Lancet 367:1262-1270.

Johnson JA, Zatorre RJ (2006) Neural substrates for dividing and focusing attention between simultaneous auditory and visual events. Neuroimage 31:1673-1681.

Kaplan EF, Goodglass H, Weintraub S (1983) The Boston Naming Test (2nd edition). Philadelphia, PA: Lea & Febiger.

Lim HK, Juh R, Pae CU, Lee BT, Yoo SS, Ryu SH, Kwak KR, Lee C, Lee CU (2008) Altered verbal working memory process in patients with Alzheimer's disease: an fMRI investigation. Neuropsychobiology 57:181-187.

Logan GD (1988) Toward an Instance Theory of Automatization. Psychological review 95:492-527.

Loose R, Kaufmann C, Auer DP, Lange KW (2003) Human prefrontal and sensory cortical activity during divided attention tasks. Hum Brain Mapp 18:249-259.

Mattis S (1976) Mental status examination for organic mental syndrome in the elderly patient. In: Geriatric Psychiatry (Bellak L, Karasu TB, eds), pp 77–121. New York: Grune & Stratton.

McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984) Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 34:939-944.

Middleton FA, Strick PL (1994) Anatomical evidence for cerebellar and basal ganglia involvement in higher cognitive function. Science 266:458-461.

Middleton FA, Strick PL (2000) Basal ganglia output and cognition: evidence from anatomical, behavioral, and clinical studies. Brain Cogn 42:183-200.

Monchi O, Petrides M, Strafella AP, Worsley KJ, Doyon J (2006) Functional role of the basal ganglia in the planning and execution of actions. Ann Neurol 59:257-264.

Nagano-Saito A, Leyton M, Monchi O, Goldberg YK, He Y, Dagher A (2008) Dopamine depletion impairs frontostriatal functional connectivity during a set-shifting task. J Neurosci 28:3697-3706.

Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H (2005) The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 53:695-699.

Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E (1999) Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 56:303-308.

Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV, Ritchie K, Rossor M, Thal L, Winblad B (2001) Current concepts in mild cognitive impairment. Arch Neurol 58:1985-1992.

Prvulovic D, Van de Ven V, Sack AT, Maurer K, Linden DE (2005) Functional activation imaging in aging and dementia. Psychiatry Res 140:97-113.

Rajah MN, D'Esposito M (2005) Region-specific changes in prefrontal function with age: a review of PET and fMRI studies on working and episodic memory. Brain 128:1964-1983.

Ranganath C, Cohen MX, Brozinsky CJ (2005) Working memory maintenance contributes to long-term memory formation: neural and behavioral evidence. J Cogn Neurosci 17:994-1010.

Regard M (1981) Cognitive rigidity and flexibility: a neuropsychological study. In: University of Victoria, Canada.

Rey A (1959) Test de copie d'une figure complexe: manuel. Paris: Les éditions du centre de psychologie appliquée.

Royall DR, Palmer R, Chiodo LK, Polk MJ (2005) Executive control mediates memory's association with change in instrumental activities of daily living: the Freedom House Study. J Am Geriatr Soc 53:11-17.

Schubert T, Szameitat AJ (2003) Functional neuroanatomy of interference in overlapping dual tasks: an fMRI study. Brain Res Cogn Brain Res 17:733-746.

Signoret JL (1991) Batterie d'efficience mnésique BEM 144. Paris: Elsevier.

Smith EE, Jonides J (1999) Storage and executive processes in the frontal lobes. Science 283:1657-1661.

Szameitat AJ, Schubert T, Muller K, Von Cramon DY (2002) Localization of executive functions in dual-task performance with fMRI. J Cogn Neurosci 14:1184-1199.

Van der Linden M, Adam S, Agniel A, Baisset-Mouly C, Bardet F, Coyette F, Desgranges B, Deweer B, Ergis AM, Gély-Nargeot MC, Grimomprez L, Juillerat

AC, Kalafat M, Poitrenaud J, Sellal F, Thomas-Antérion C (2004) L'évaluation de troubles de la mémoire: présentation de quatre tests de mémoire épisodique (avec étalonnage). Marseille: Solal.

Wager TD, Smith EE (2003) Neuroimaging studies of working memory: a meta-analysis. Cogn Affect Behav Neurosci 3:255-274.

Wechsler D (1997) *Wechsler Adult Intelligence Scale-III.* New York: Psychological Corporation.

Winblad B et al. (2004) Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J Intern Med 256:240-246.

Yetkin FZ, Rosenberg RN, Weiner MF, Purdy PD, Cullum CM (2005) FMRI of working memory in patients with mild cognitive impairment and probable Alzheimer's disease. Eur Radiol.

Table 1

Demographic variables and scores on the neuropsychological tasks for the three groups.

	Controls	MCI higher-cognition	MCI lower-cognition
	n = 14	n = 12	n = 12
Gender	8F/6M	7F/5M	7F/5M
Age	67.21 (6.80)	68.50 (10.82)	68.33 (6.91)
Education	14.57 (3.76)	14.92 (3.92)	14.08 (4.23)
MDRS	140.33 (2.65)	139.58 (2.23)	130.17 (4.90)[c,f]
MMSE	29.29 (1.14)	28.92 (1.68)	27.00 (1.81)[b,e]
MOCA	27.64 (1.39)		
SMAF		-0.82 (0.90)	-1.46 (1.18)
Boston Naming Test		13.92 (1.16)	12.58 (1.73)
Coding (WAIS-III)	11.29 (2.30)	10.58 (2.35)	8.75 (2.60)[a]
Benton Judgment of line orientation		25.17 (3.64)	23.25 (3.44)
Copy of Rey's Figure (score)		31.50 (3.23)	30.42 (3.59)
Immediate recall of Rey's Figure (score)		13.91 (5.51)	8.67 (6.21)[d]
Delayed recall of Rey's Figure (score)		14.67 (4.93)	8.13 (5.92)[e]
Stroop 3rd plate (errors)		0.92 (1.08)	1.92 (2.57)
RL/RI-16 3rd free recall	12.21 (2.32)	10.33 (2.77)	6.08 (2.50)[c,f]
RL/RI-16 delayed free recall	12.71 (2.40)	9.00 (4.80)[a]	5.75 (3.19)[c]

Note. SD are in parentheses. [a] impairment relative to controls at $p < .05$; [b] impairment relative to controls at $p < .01$; [c] impairment relative to controls at $p < .001$; [d] impairment relative to MCI higher-cognition at $p < .05$; [e] impairment relative to MCI higher-cognition at $p < .01$; [f] impairment relative to MCI higher-cognition at $p < .001$

Table 2

Clusters (>10 voxels) significantly more activated during the manipulation task than during the control task for healthy controls, MCI higher-cognition and MCI lower-cognition with cluster size, peak voxel MNI coordinates and corresponding t-values.

Activated areas (Brodmann area) ($p < .001$, uncorrected)	Cluster Size	x	y	z	t-value
Healthy controls: Manipulation > control task					
Left occipitoparietal areas (7, 19, 39, 40)	275	-27	-78	42	5.57
Left/Right cerebellum	770	9	-75	-27	5.52
Right inferior frontal gyrus (45, 47)	80	33	27	0	5.27
Left superior and medial frontal gyri and left cingulate gyrus (6, 8, 32)	46	-6	12	48	5.06
Left inferior and middle frontal gyri (6, 9)	39	-45	-3	39	4.64
Left inferior frontal gyrus (44)	18	-51	6	18	4.42
Left inferior frontal gyrus (45, 46)	93	-39	21	18	4.32
Right superior and medial frontal gyri and right cingulate gyrus (6, 8, 32)	17	9	24	45	4.00
Right inferior and superior parietal lobules and precuneus (7, 40)	34	36	-51	51	3.74
Left precuneus (7)	18	-6	-81	45	3.65
Right occipital areas (19)	11	33	-72	42	3.61
Right precuneus (7)	14	18	-72	48	3.59
MCI higher-cognition: Manipulation > control task					
Left inferior frontal gyrus (44, 45, 47)	156	-30	24	3	5.82

Left occipitoparietal areas (7, 19, 39)	241	-30	-60	39	5.19
Left/Right superior and medial frontal gyri and left cingulate gyrus (6, 8, 24, 32)	136	-6	12	48	4.70
Right occipitoparietal areas (19, 39)	30	36	-75	33	4.52
Right cerebellum	26	12	-66	-30	4.21
Left middle and superior frontal gyri (6, 8)	54	-24	12	60	4.16
Left inferior parietal lobule (40)	15	-45	-45	45	4.08
MCI lower-cognition: Manipulation > control task					
Left/Right superior and medial frontal gyri and left cingulate gyrus (6, 8, 32)	136	-3	9	57	4.54
Right cerebellum	53	33	-60	-30	4.12
Right medial frontal gyrus and right cingulate gyrus (8, 9, 32)	16	6	30	39	3.61

Table 3

Clusters (>10 voxels) significantly more activated during the divided attention task than during the manipulation and control tasks for healthy controls, MCI higher-cognition and MCI lower-cognition with cluster size, peak voxel MNI coordinates and corresponding t-values.

Activated areas (Brodmann area) ($p < .001$, uncorrected)	Cluster Size	x	y	z	t-value
Healthy controls: Divided attention > manipulation & control tasks					
Left/Right precuneus and posterior cingulate gyrus (7, 31)	662	6	-69	33	5.77
Left precuneus (7)	10	-3	-48	54	3.91
MCI higher-cognition: Divided attention > manipulation & control tasks					
Left inferior frontal gyrus, left caudate, and left putamen (47)	697	-12	9	0	5.74
Left/Right precuneus and left posterior cingulate gyrus (7, 31)	521	21	-45	72	5.23
Left cerebellum	35	-24	-54	-42	5.05
Left middle temporal gyrus (21)	52	-45	-3	-18	4.34
Right entorhinal & perirhinal areas (28, 35)	16	21	-27	-15	4.25
Left/Right anterior cingulate cortex (24, 32)	50	0	36	9	4.16
Right posterior cingulate cortex (31)	17	15	-57	21	4.07
Right paracentral lobule (5)	12	6	-42	54	4.07
Left occipitotemporal areas (36, 37)	111	-42	-39	-18	4.00
Right inferior parietal lobule, supramarginal and angular gyri (39, 40)	28	45	-57	27	3.87

Right superior frontal gyrus (6)	14	24	-9	69	3.57
MCI lower-cognition: Divided attention > manipulation & control tasks					
Left/Right precuneus and posterior cingulate gyrus (7, 23, 31)	471	-6	-69	24	5.83
Left temporoparietal areas (22, 39)	59	-48	-63	21	5.03
Right temporoparietal areas (39)	13	48	-66	24	4.04
Right precuneus (7)	11	12	-69	33	3.85

Table 4

Clusters (cluster-level correction at $p < .05$) significantly more activated in healthy controls than in MCI higher- and lower-cognition or significantly more activated in MCI higher- and lower-cognition than in healthy controls for the manipulation task, with cluster size, peak voxel MNI coordinates, corresponding t-values and correlations with task performances.

Activated areas (Brodmann area) ($p < .001$, uncorrected)	Cluster Size	x	y	z	t	correlation
Manipulation: MCI higher-cognition > Healthy controls						
Left postcentral gyrus (43)	34	-48	-12	21	4.45	0.27
Left middle and superior frontal gyri (6, 8)	48	-39	18	48	4.44	0.21
Manipulation: Healthy controls > MCI higher-cognition						
Left cerebellum	145	-42	-66	-24	5.32	0.51
Manipulation: MCI lower-cognition > Healthy controls						
None						
Manipulation: Healthy controls > MCI lower-cognition						
Left inferior and middle frontal gyri (45, 46)	42	-42	30	18	4.46	0.26
Left occipitotemporal areas (19, 37)	39	-48	-66	-12	3.91	-0.07

Table 5

Clusters (>10 voxels) significantly more activated in healthy controls than in MCI higher- and lower-cognition or significantly more activated in MCI higher and lower-cognition than in healthy controls for the divided attention task, with cluster size, peak voxel MNI coordinates, corresponding t-values and correlations with task performances.

Activated areas (Brodmann area) ($p < .001$, uncorrected)	Cluster Size	x	y	z	t	correlation
Divided attention: MCI higher-cognition > Healthy controls						
Left/Right anterior cingulate cortex, left caudate, left putamen, left insula, and left inferior frontal gyrus (13, 25, 47)	777	-9	9	-3	5.29	0.62*
Left fusiform gyrus (36, 37)	66	-36	-42	-15	4.74	0.31
Left thalamus	52	-6	-15	18	4.42	0.48
Left cerebellum and midbrain	32	-6	-39	-21	4.02	0.49
Right putamen	30	24	15	-6	3.74	0.32
Divided attention: Healthy controls > MCI higher-cognition						
None						
Divided attention: MCI lower-cognition > Healthy controls						
None						
Divided attention: Healthy controls > MCI lower-cognition						
None						

Note. * correlation significant at $p < .05$

Figure Captions

Figure 1. Mean percentage of correctly solved equations in the manipulation task for the healthy controls, MCI higher-cognition and MCI lower-cognition groups. Note. * $p < .05$.

Figure 2. Divided attention cost score for both the mean percentage of correctly solved equations and the correctly detected red targets for the healthy controls, MCI higher-cognition and MCI lower-cognition groups. Note. * $p < .05$.

Figure 3. Regions significantly more activated in MCI individuals than in healthy controls (red) or significantly more activated in healthy controls than in MCI individuals (blue) during the manipulation task.

Figure 4. Regions significantly more activated in MCI individuals than in healthy controls (red) or significantly more activated in healthy controls than in MCI individuals (blue) during the divided attention task.

Figure 1. Mean percentage of correctly solved equations in the manipulation task for the healthy controls, MCI higher-cognition and MCI lower-cognition groups.

Note. * $p < .05$.

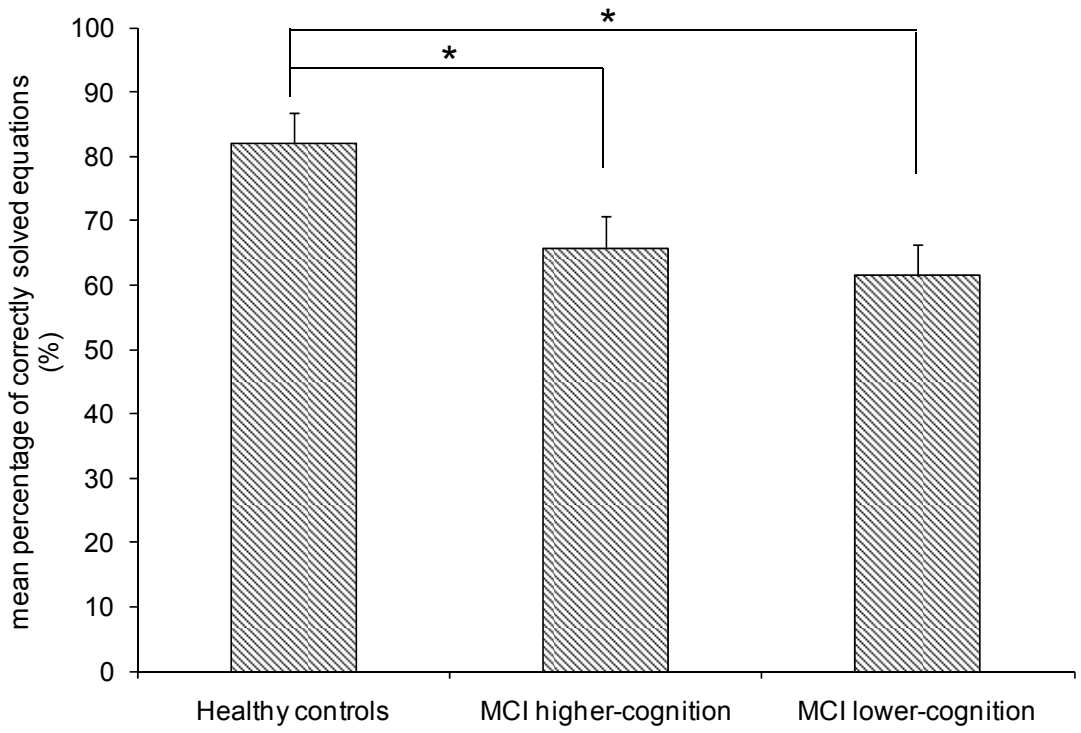


Figure 2. Divided attention cost score for both the mean percentage of correctly solved equations and the correctly detected red targets for the healthy controls, MCI higher-cognition and MCI lower-cognition groups. Note. * $p < .05$.

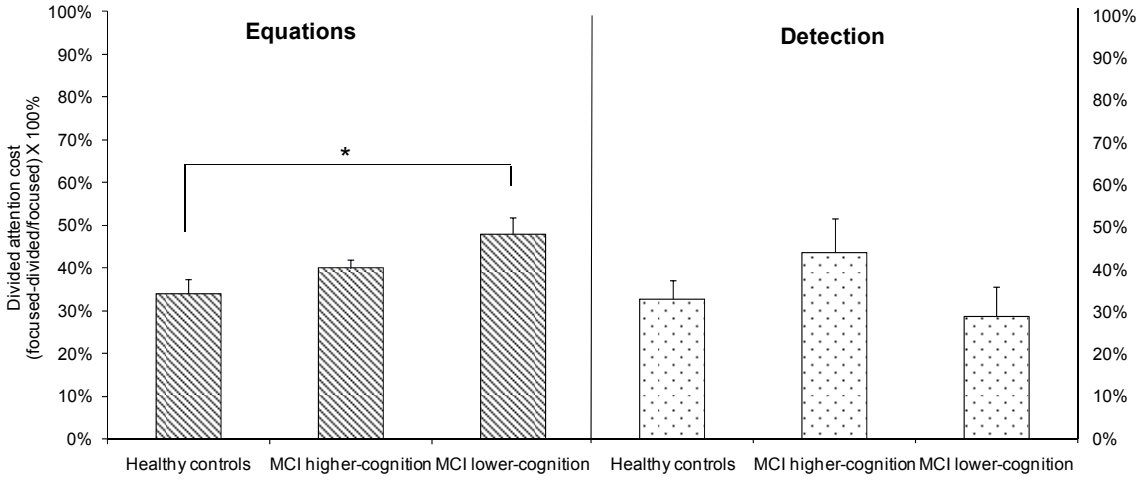


Figure 3. Regions ($p < .001$, uncorrected, cluster size > 10 voxels) more activated in MCI individuals than in healthy controls (red) or more activated in healthy controls than in MCI individuals (blue) during the manipulation task.

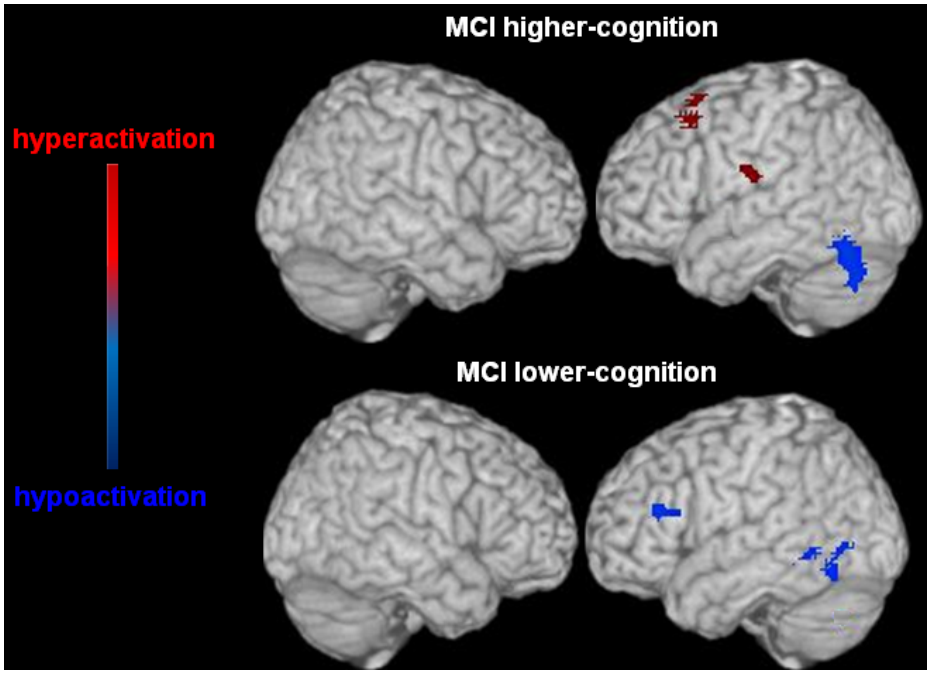
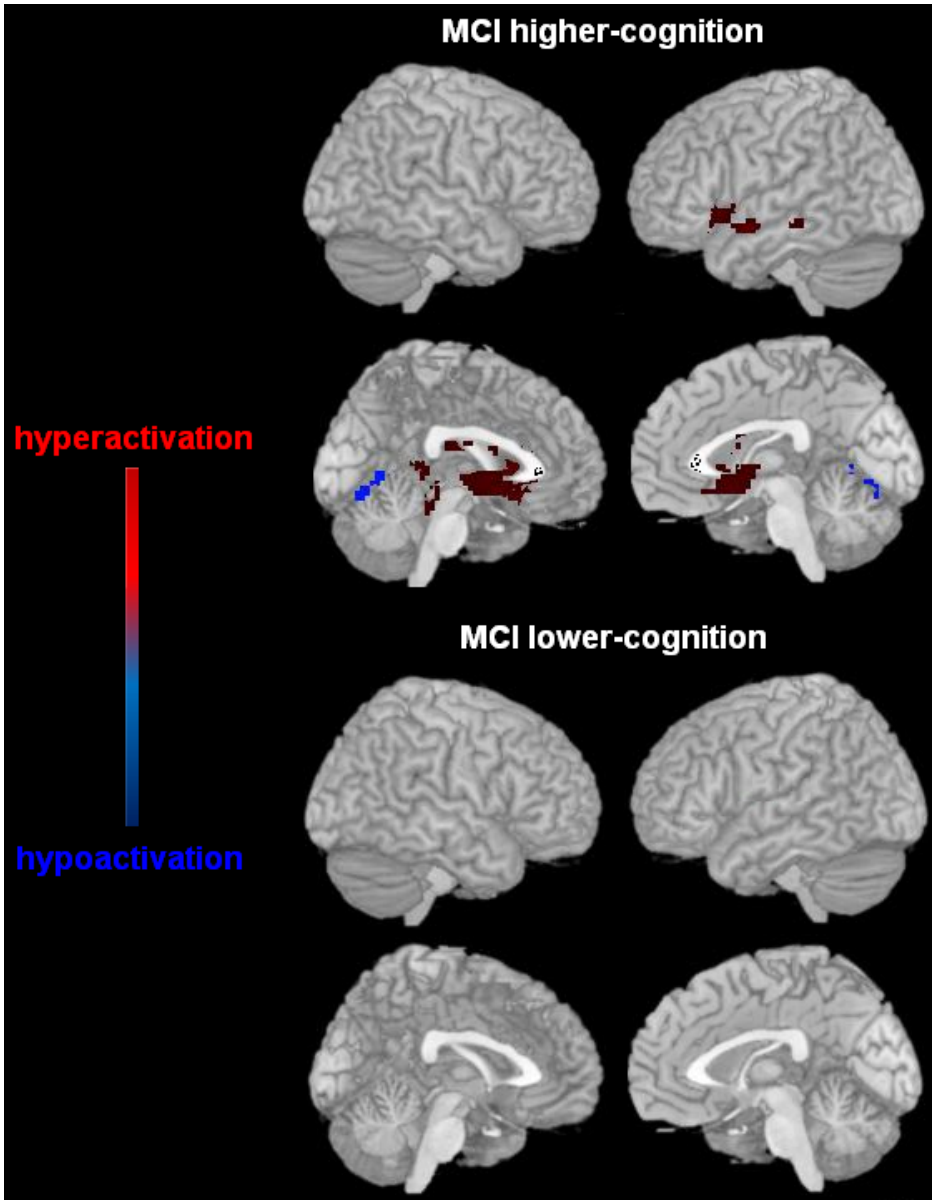


Figure 4. Regions (p < .001, uncorrected, cluster size > 10 voxels) more activated in MCI individuals than in healthy controls (red) or more activated in healthy controls than in MCI individuals (blue) during the divided attention task.



CHAPITRE 7

Discussion générale

7.1 Rappel et discussion des principaux résultats

Le but de cette thèse était d'étudier les activations fonctionnelles associées à la mémoire épisodique et à la mémoire de travail dans le trouble cognitif léger (TCL). La thèse comportait deux sous-objectifs, soit l'étude de l'effet de la sévérité de la maladie sur les patrons d'activations cérébraux des TCL, ainsi que l'étude des caractéristiques de la tâche sur ces patrons. Pour ce faire, nous avons administré à des personnes âgées saines et à des personnes TCL différentes tâches cognitives portant sur l'encodage et la récupération de matériel verbal. De plus, nous avons ajouté des tâches de mémoire de travail qui mesurent la manipulation d'information et la division de l'attention. Ces études ont mis en évidence une interaction entre le niveau de sévérité de la maladie et les processus cognitifs impliqués dans la tâche.

Avant de mesurer les activations propres au TCL, nous avons évalué la fiabilité du signal IRMf chez les personnes TCL et chez les individus âgés sains (se référer à l'étude intitulée « Test-retest reliability of fMRI verbal episodic memory paradigms in healthy older adults and in persons with mild cognitive impairment »). Une bonne fiabilité du signal est essentielle à l'utilisation de l'IRMf comme marqueur de progression de la maladie ou encore comme outil pour mesurer l'effet des interventions. Dix personnes âgées saines et dix personnes TCL ont pris part à cette expérience. Des tâches d'encodage et de récupération de mots ainsi que de traitement phonologique, la lecture de pseudomots, ont été administrées aux participants à deux reprises, à six semaines d'intervalle. La reproductibilité a été mesurée à partir d'un ratio de chevauchement des voxels selon 4 seuils statistiques différents, de comparaisons statistiques des conditions d'une session à une autre, d'ANCOVAs et de corrélations

intra-classes. Les résultats ont montré une bonne reproductibilité au niveau des comparaisons de groupes (comparaisons statistiques des conditions d'une session à une autre et ANCOVAs). Ainsi, les différences d'activation observées entre les personnes âgées saines et les TCL sont similaires après six semaines d'intervalle. De plus, cette étude indique que les personnes âgées saines et les TCL montrent, en tant que groupes, un niveau de fiabilité similaire. Ces résultats diffèrent de ce qui a été noté chez les patients atteints de schizophrénie (Manoach et al., 2001), d'épilepsie (Fernandez et al., 2003), d'aphasie non fluente chronique (Kurland et al., 2004) et d'un accident vasculaire cérébral (Chen & Small, 2007), où le niveau de fiabilité tendait à être inférieur à celui du groupe contrôle. Ceci pourrait s'expliquer par le fait que le TCL n'est probablement pas une pathologie très variable dans un court laps de temps, peu de variabilité intra-individuelle, et qu'on ne s'attend ainsi pas à une dégénération ou une récupération significative durant un intervalle de six semaines. Ces résultats valident l'approche adoptée dans nos autres études, car ils révèlent que le début de la MA n'altère pas la reproductibilité du signal et qu'il est ainsi possible de comparer le patron d'activation des personnes âgées saines et des TCL. De plus, ces résultats indiquent que l'IRMf pourrait être utilisé comme outil pour mesurer les effets d'interventions pharmacologiques (Petersen et al., 2005) ou de stratégies préventives (Belleville et al.; Belleville et al., 2006) chez les personnes portant un diagnostic de maladie d'Alzheimer (MA) ou à risque de développer la maladie. Il faut néanmoins souligner que la reproductibilité du signal était beaucoup plus faible au niveau individuel (corrélations intra-classes). Ainsi, les individus montrent une assez grande variabilité dans leur signal IRMf d'une session à une autre, mais cette variabilité semble s'amoindrir lorsqu'on regroupe les participants. L'utilisation d'une méthodologie reposant sur des études de cas ou des études de cas

multiples pour évaluer l'efficacité d'un traitement pose donc un défi particulier en raison de la faible reproductibilité du signal à un niveau individuel. En revanche, cette étude supporte le recours à une méthodologie faisant appel à des études de groupe.

Le but de l'article intitulé « Functional neuroanatomy of the encoding and retrieval processes of verbal episodic memory in MCI » était de comparer le patron d'activation cérébral des personnes âgées saines et des personnes TCL. De plus, nous voulions déterminer s'il y avait un effet de sévérité sur ces différences d'activation. Pour ce faire, une tâche d'encodage et de récupération de mots et de pseudo-mots a été administrée à 10 personnes âgées saines et à 12 TCL. Même si aucune différence de performance n'a été notée entre les deux groupes de participants, plusieurs différences d'activation ont été observées, tout particulièrement durant l'encodage. En effet, les TCL ont montré plusieurs hypoactivations dans des régions qui sont connues, chez les patients MA, comme étant souvent compromises structurellement ou montrant de l'hypométabolisme à la TEP comme par exemple dans les gyri temporaux moyens et supérieurs. Nos résultats indiquent également des zones d'hyperactivation, dont l'une d'entre elle, le cortex préfrontal ventrolatéral, a montré une corrélation positive avec le niveau de performance des participants. Étant donné le nombre restreint de participants dans cette étude, l'effet de la sévérité a été mesuré en corrélant le signal dépendant du niveau d'oxygénation cérébrale (signal BOLD) des régions hyper- ou hypoactivées chez les MCI à leurs scores sur une échelle de fonctionnement cognitif global, la MDRS. Une corrélation positive a été obtenue pour deux des régions hypoactivées chez les TCL, les gyri temporaux moyens et supérieurs. Ainsi, les TCL les plus atteints cognitivement (faible score au MDRS) ont montré moins d'activation dans ces régions que ceux moins

atteints au plan cognitif. En somme, ces résultats nous ont permis de constater que les personnes âgées saines et les personnes TCL n'ont pas le même patron d'activation cérébral lors de l'exécution d'une tâche de mémoire et qu'ils montrent à la fois des hyperactivations et des hypoactivations. La présence d'hypoactivation était attendue puisqu'elle est généralement rapportée dans la maladie d'Alzheimer. En revanche, la présence d'hyperactivaiton pourrait être une caractéristique des stades les plus légers de la maladie et particulièrement, le TCL.

Le but de l'article intitulé « Compensation and disease severity on the memory-related activations in mild cognitive impairment » était d'évaluer directement cette hypothèse en examinant si la sévérité du TCL modulait le patron d'activation cérébral. Pour cela, le score médian du groupe de TCL au test de MDRS a été utilisé pour déterminer un groupe de TCL plus atteints (score inférieur à la médiane du groupe) et un groupe de TCL moins atteints (score supérieur à la médiane du groupe). Cette procédure nous a permis de tester l'effet de sévérité d'une manière plus précise que dans l'étude précédente qui faisait appel à une analyse corrélationnelle. En effet, le fait de séparer les participants en deux groupes permet d'évaluer si les conditions de la tâche modulent les changements d'activation. Une tâche d'encodage associatif composée de deux conditions, un encodage de paires de mots reliés sémantiquement et un encodage de paires de mots non-reliés sémantiquement, a été administrée aux participants. Les résultats indiquent que les TCL plus atteints ont des performances inférieures à celles des groupes de contrôles et de TCL moins atteints. Les données en neuroimagerie montrent que les TCL moins atteints montrent des hyperactivations au niveau du cortex préfrontal, de l'hippocampe gauche et des aires postérieures, des aires connues pour leur implication

dans les fonctions mnésiques (Cabeza & Nyberg, 2000). De manière intéressante, la condition d'encodage de paires de mots reliés sémantiquement a été la seule à entraîner une hyperactivation du cortex préfrontal ventrolatéral chez les TCL moins atteints. Cette région est connue pour son implication dans l'élaboration sémantique (Fletcher & Henson, 2001; Poldrack et al., 1999) et dans l'encodage de paires de mots liés sémantiquement (Kapur et al., 1996). Ce résultat est important, car il indique que les mécanismes compensatoires utilisés par les TCL ne sont pas fixes, mais varient selon le processus cognitif impliqué dans la tâche. Les TCL moins atteints n'ont pas montré d'hyperactivations dans le cortex préfrontal et ils ont même montré des hypoactivations dans les aires postérieures. Ces résultats confirment ainsi notre hypothèse qu'il y a présence de mécanismes compensatoires durant les premiers stades du TCL et que ces mécanismes compensatoires ne sont plus présents lorsque les atteintes cognitives deviennent plus importantes.

L'article intitulé « Effect of disease severity on neural compensation of item and associative recognition in mild cognitive impairment » avait comme objectif de vérifier si les mêmes processus étaient présents pendant la phase de récupération d'information en mémoire. Il permettait ainsi de vérifier si le phénomène se généralisait à d'autres processus mnésique. Les deux groupes de TCL, les plus atteints et les moins atteints, et le groupe de personnes âgées saines ont réalisé une tâche de reconnaissance comprenant une condition dans laquelle les paires de mots à la récupération étaient soit intactes, soit recombinées (censée mesurer les processus de familiarité et de recollection) et une condition dans laquelle les paires étaient soit intactes, soit nouvelles (censée mesurer uniquement le processus de familiarité). Nous faisons l'hypothèse que la première

condition impliquait un processus cognitif altéré plus précocement dans le TCL, la recollection, tandis que la deuxième reposait sur un processus cognitif altéré plus tardivement dans le TCL, la familiarité. Les résultats indiquent que les trois groupes ont des performances plus basses pour la tâche de paires de mots intactes/recombinées que pour la tâche intactes/nouvelles et que les TCL plus atteints ont des performances inférieures à celles des groupes de contrôles et de TCL moins atteints. Les données de neuroimagerie indiquent que les TCL moins atteints ont effectivement montré des hyperactivations uniquement durant la condition de recollection tandis que les TCL plus atteints ont montré des hyperactivations uniquement durant la condition de familiarité. De manière intéressante, ces hyperactivations étaient principalement situées dans des régions cérébrales typiquement associées à la récupération d'information en mémoire, telles que le cortex préfrontal et le lobule pariétal inférieur gauche. Ainsi, cette étude a également montré que les mécanismes compensatoires dépendent du degré d'atteinte du processus cognitif étudié. Ces résultats sont importants, car ils nous indiquent qu'il y a de la plasticité neuronale durant tout le stade du TCL, mais que la mise en branle de ces mécanismes dépend du type de processus cognitif impliqué. Ainsi, au fur et à mesure que les personnes TCL progressent vers la MA, on observe une dégradation de leurs mécanismes compensatoires pour la recollection avec une émergence des mécanismes de compensation pour la familiarité. Ceci pourrait s'expliquer par le fait que les neuropathologies caractéristiques de la MA affectent très rapidement les régions impliquées dans les processus de recollection, mais n'affectent que plus tardivement les aires impliquées dans les processus de familiarité (Arnold, Hyman, Flory, Damasio, & Van Hoesen, 1991; Braak & Braak, 1995).

Enfin, l'article « Emergence and breakdown of neural plasticity during mild cognitive impairment » avait comme objectif d'étendre ces hypothèses à une autre fonction cognitive touchée dans le TCL et la MA: les processus exécutifs en MdeT. Ainsi, deux tâches impliquant des composantes différentes des fonctions exécutives, soit la manipulation de l'information et l'attention divisée, ont été administrées à deux groupes de 12 TCL chacun et à un groupe de 14 personnes âgées saines. Les résultats indiquent la présence d'hyperactivations chez les TCL moins atteints lors de l'exécution des deux tâches et ce, tout particulièrement dans les aires préfrontales gauches. De plus, des analyses corrélationnelles ont montré une association positive entre l'hyperactivation d'un réseau frontostriatal chez les TCL moins atteints et leurs performances à la tâche. Ces résultats suggèrent que ce réseau frontostrial pourrait être le fruit d'une réorganisation fonctionnelle de nature compensatrice. Le groupe de TCL plus atteint a obtenu un tout autre patron d'activation: ils n'ont pas montré d'hyperactivations durant la tâche d'attention divisée et ils n'ont montré que des hypoactivations lors de la tâche de manipulation. Ces données sont importantes, car elles montrent que les mécanismes compensatoires observés en début de TCL, ainsi que leur dégradation dans les stades plus avancés du TCL, ne se limitent pas aux fonctions mnésiques mais touchent aussi les fonctions exécutives. Cette incapacité à compenser lors des tâches exécutives chez les TCL plus atteints pourrait ainsi exacerber leurs troubles mnésiques (Ranganath, Johnson, & D'Esposito, 2000) et représenter ainsi le facteur critique dans la progression du TCL vers la démence (Royall, Palmer, Chiodo, & Polk, 2005).

7.2 Mécanismes compensatoires

Les résultats de nos études pointent vers une prédominance des hyperactivations chez les TCL les moins atteints qui, selon notre hypothèse, serait les TCL en début de continuum. Une telle présence des hyperactivations dans un groupe de participants, comparativement à un groupe contrôle, a été interprétée comme étant soit premièrement de la dédifférentiation, c'est-à-dire un recrutement non-sélectif reflétant une dispersion généralisée de l'activation dans des régions non pertinentes pour la tâche (Li & Lindenberger, 1999; Logan, Sanders, Snyder, Morris, & Buckner, 2002), soit deuxièmement des mécanismes permettant de compenser les déficits liés à la lésion et ainsi améliorer les performances (Cabeza, Anderson, Locantore, & McIntosh, 2002; Grady et al., 2003; Grady, McIntosh, & Craik, 2005). Un des modèles de compensation les plus influants chez les personnes âgées est le modèle HAROLD (Hemispheric Asymmetry Reduction in OLDer adults). Cette théorie soutient que les jeunes ont tendance, lors de la mise en place de mécanismes compensatoires, à activer un des deux lobes préfrontaux de manière proéminente durant l'exécution de tâches cognitives (apprentissage, récupération en mémoire à long terme, mémoire de travail, fonctions exécutives et perception) tandis que les personnes âgées ont plutôt tendance à activer le cortex préfrontal de manière bilatérale. De manière intéressante, cette bilatéralisation des activations est uniquement observée chez les personnes âgées montrant des performances à un niveau similaire à celui des jeunes. Ainsi, il semble important de vérifier si les hyperactivations s'accompagnent d'augmentation ou de baisse de performances à la tâche si l'on désire déterminer si elles sous-tendent des mécanismes compensatoires ou de la dédifférentiation. Dans le cas de nos études, le fait que les MCI moins atteints ont obtenu des performances comparables à celles des participants contrôles suggère que

leurs hyperactivations représentent des mécanismes de compensation. Cela est également corroboré par la présence d'une corrélation positive entre l'hyperactivation des TCL moins atteints et leurs performances à la tâche dans deux de nos études.

Bien qu'il y ait un certain consensus sur les circonstances où des hyperactivations puissent être interprétées comme reflétant des mécanismes compensatoires, la localisation de l'aire compensatrice semble toutefois dépendre du modèle (Banich, 1998; Cabeza, 2002; Edelman & Gally, 2001; Price & Friston, 2002; Prvulovic, Van de Ven, Sack, Maurer, & Linden, 2005). En effet, certains stipulent que les hyperactivations devraient se trouver dans des régions impliquées dans la fonction cognitive: une plus grande activation du réseau requis pour la tâche permettrait ainsi de préserver un certain niveau de performance. D'autres modèles croient plutôt que les hyperactivations devraient se trouver dans un réseau alternatif composé de structures qui ne sont normalement pas activées chez les sujets contrôles lors de l'exécution de cette tâche. Ce réseau alternatif viendrait ainsi supporter le réseau actuel en augmentant le nombre d'aires cérébrales participant à la tâche ou en permettant l'utilisation d'une autre stratégie cognitive. Il apparait ainsi intéressant de s'interroger sur la localisation des hyperactivations des TCL moins atteints et de vérifier si elle dépend de la fonction cognitive impliquée ou si, au contraire, un seul réseau alternatif sert toujours de mécanisme compensatoire pour toutes les tâches.

Une analyse des divers résultats des études de cette thèse pointent vers une certaine tendance en ce qui concerne la localisation des régions impliquées dans les mécanismes compensatoires. En effet, il semblerait que les régions hyperactivées par les

TCL moins atteints sont principalement dans des régions impliquées dans l'exécution de la tâche (c-à-d. activées par les contrôles) et semblent ainsi différer selon le type de processus cognitif impliqué. À titre d'exemple, les deux régions hyperactivées par les TCL dans la deuxième étude (le gyrus préfrontal inférieur gauche et le cortex prémoteur gauche) étaient toutes deux des structures déjà activées par les contrôles. Des résultats similaires ont été observés dans les autres études, mais la localisation des régions différait selon la fonction cognitive impliquée dans la tâche. Une deuxième tendance qui émerge de nos résultats est qu'en plus des régions impliquées dans la tâche, des activations additionnelles dans le lobe frontal ont été observées dans toutes nos études. Ainsi, l'hyperactivation du cortex préfrontal ne semble pas dépendre de la fonction cognitive impliquée. Il est donc possible que les aires préfrontales jouent un rôle particulier dans la compensation et que leurs hyperactivations reflètent l'implantation d'un réseau compensatoire pouvant supporter la plupart des processus cognitifs. Il est aussi intéressant que, lors de la troisième étude, les TCL moins atteints n'ont pas seulement activé les mêmes aires préfrontales que les contrôles dans l'hémisphère gauche, mais ils ont aussi activé ces mêmes aires dans l'hémisphère droit. Ces résultats sont ainsi en accord avec le modèle HAROLD et suggère qu'une activation bilatérale des régions frontales puisse servir de mécanisme compensatoire aussi bien chez les personnes âgées saines que chez celles qui sont possiblement en phase prodromale d'une démence.

7.3 Hypoactivations

Le TCL étant un prodrome de la MA, on pourrait s'attendre à ce que les hypoactivations observées chez les TCL plus atteints, c'est-à-dire ceux qui sont

probablement les plus près du moment de progression vers la MA, soient principalement situées dans des aires connues pour leur accumulation de neuropathologies (plaques amyloïdes ou protéine Tau) lors du développement de la maladie. Ainsi, si l'on se fie aux études ayant fait des autopsies sur des patients MA décédés, les hypoactivations devraient se situer principalement dans les aires temporales médiales ainsi que dans le cortex associatif (aires préfrontales et pariétales, lobe temporal latéral et cortex cingulé) (Arnold et al., 1991; Braak & Braak, 1991). Il est intéressant de noter que ces régions sont aussi celles qui ont montré la plus grande quantité de marqueur de plaques amyloïdes, le Pittsburgh Compound B, chez des personnes TCL et des patients MA (Frisoni et al., 2009; Kemppainen et al., 2007; Klunk et al., 2004; Rowe et al., 2007).

En général, la très grande majorité des hypoactivations des TCL observées dans nos études se trouvaient effectivement dans des régions connues pour leur atteinte dans la MA (ex. : lobule pariétale inférieur gauche, cortex cingulé et cortex préfrontal médial). Cette observation est compatible avec le modèle de Prvulovic et ses collègues (2005) qui stipule qu'un dommage important à une région diminue tant sa capacité de réserve, que de traitement. La région atteindrait ainsi beaucoup plus rapidement son niveau d'activation maximale et elle montrerait donc généralement un niveau d'activation inférieur à celui des sujets sains, sauf pour les tâches peu exigeantes. Ce modèle est entièrement compatible avec nos résultats: nous avons trouvé des hypoactivations dans des régions possiblement endommagées chez les TCL les plus atteints lors de toutes les tâches cognitives, excepté la moins exigeante (familiarité). Il serait intéressant d'utiliser des marqueurs de plaques amyloïdes et de voir s'il y a une association entre le niveau d'atteinte pathologique d'une région et son hypoactivation.

7.4 Limitations

Les études rapportées ici présentent certaines limitations communes qui doivent être gardées à l'esprit lors de l'interprétation des résultats. Premièrement, toutes ces études ont été faites selon un devis transversal plutôt que longitudinal. Il sera ainsi important de reproduire les résultats d'effet de sévérité en suivant un groupe de sujets TCL pendant quelques années et en montrant un changement des hyperactivations pour des hypoactivations chez ces mêmes sujets. Une autre limitation concerne la possibilité que certaines de nos personnes TCL ne soient pas dans une phase prodromale de la MA, mais plutôt des personnes âgées « saines » qui ont toujours montré des capacités mnésiques inférieures au reste de la population. Cependant, il faut souligner le fait que les critères TCL utilisés dans nos études ne comprenaient pas uniquement des critères psychométriques, mais aussi la présence d'une plainte mnésique, préférablement corroborée par un proche. La présence d'une plainte augmente ainsi la probabilité que les déficits mnésiques soient récents et qu'il dénote ainsi d'une certaine détérioration cérébrale. Il serait bon de noter le fait que plus de 50% de nos TCLs ont montré un déclin cognitif ou une progression vers la MA après seulement deux ans de suivi. Ce taux de progression est semblable à ce qui est observé dans les autres laboratoires ou cliniques (Gauthier et al., 2006) et suggère ainsi qu'une proportion importante de nos TCL sont possiblement atteints d'un processus dégénératif. Par ailleurs, cette dégénérescence des fonctions mnésiques a été observée dans les deux sous-groupes de TCL, ce qui rend peu probable l'hypothèse que nos TCL les moins atteints soient des personnes âgées saines avec de faibles capacités mnésiques et que nos TCL les plus atteints représentent les seuls « vrai TCL ». Nous croyons plutôt que le stade du TCL représente un continuum et

qu'il est ainsi possible d'identifier des personnes qui soient assez éloignées de la progression vers la démence et d'en identifier d'autres qui qu'en sont pas très loin.

D'autres limitations plus techniques doivent aussi être mentionnées. Premièrement, toutes nos études IRM ont été effectuées avec un devis en bloc plutôt qu'évènementiel. Une faiblesse du devis en bloc réside dans son incapacité à comparer séparément les bonnes et les mauvaises réponses des participants, ce qui a été particulièrement utilisé avec les tâches mnésiques (Wagner et al., 1998). Toutefois, le devis en bloc comporte plusieurs avantages, dont celui d'être plus facile à suivre pour les patients présentant des difficultés cognitives étant donné que les conditions alternent moins fréquemment. De plus, ce devis offre une puissance de détection maximale, ce qui est particulièrement critique pour des études comme les nôtres où des sous-groupes de patients sont comparés entre eux et qu'on risque ainsi de retrouver des tailles d'effets plus modestes. Maintenant que des effets de sévérité et de processus cognitifs ont été montrés avec un devis en bloc, il serait intéressant d'essayer de reproduire ces résultats avec un devis évènementiel. Enfin, l'utilisation d'une échelle clinique (c-à-d. le MDRS) comme indicateur de sévérité de la maladie pourrait être critiqué. Néanmoins, nous avons préféré utilisé une échelle mesurant les déficits cognitifs globaux à des marqueurs neuroanatomiques, tel que le volume hippocampique, car les critères diagnostiques actuels de la MA repose sur des critères cliniques. Il serait toutefois intéressant d'analyser à nouveau ces données en séparant les sujets TCL selon leur volume hippocampique ou selon un marqueur de plaques amyloïdes tel que le marqueur PIB (Pittsburgh Compound B)

7.5 Implications et perspectives futures

Les résultats de cette thèse sont compatibles avec la notion d'un continuum dans le TCL où les premiers stades sont caractérisés par une émergence de mécanismes compensatoires suivi d'un effondrement de ces même processus lors des stades plus avancés. Ce continuum a plusieurs implications cliniques importantes, car il suggère que bien que toutes les personnes TCL soient à un plus grand risque de développer une MA, il est possible d'en identifier un sous-groupe qui lui est à très haut risque de progresser plus rapidement vers la maladie. D'ailleurs, après un suivi de deux ans, aucun de nos TCL moins atteints n'avaient progressé tandis que 62% (8/13) de nos TCL plus atteints avaient progressé vers une MA. Ainsi, l'utilisation du concept de sévérité chez les TCL nous permet d'avoir une meilleure idée du pronostic à court terme de ces personnes. De plus, les études de cette thèse ont montré que la dégradation des mécanismes compensatoires chez les TCL n'arrivait pas au même moment dans le continuum, mais dépendait plutôt du processus cognitif requis pour exécuter la tâche. À titre d'exemple, les personnes TCL semblent montrer une difficulté à compenser beaucoup plus tôt pour les processus de recollection et il semble ainsi important d'investiguer en profondeur les fonctions cognitives de ces personnes afin de leur offrir des recommandations qui sont centrées sur les processus cognitifs préservés. De plus, ces données suggèrent aussi que les programmes d'entraînement cognitif devraient viser des processus cognitifs où il y a encore un potentiel de compensation possible. Il pourrait ainsi être intéressant de former deux types d'entraînement cognitif pour les TCL: un pour les moins atteints qui reposerait principalement sur des mécanismes d'encodage profond, d'élaboration sémantique, de manipulation de l'information et d'aide à la recollection et un autre

programme pour les TCL plus atteints qui reposerait principalement sur du support à la familiarité et au contrôle attentionnel.

Une autre implication importante de ces études est au niveau de l'interprétation des études de neuroimagerie fonctionnelle chez les personnes TCL dans la littérature. En effet, certaines études ont identifié des hyperactivations chez les TCL tandis que d'autres ont identifié des hypoactivations. Ces données, qui semblent au premier abord comme étant divergentes, pourraient s'expliquer par un différent niveau de sévérité de leurs participants TCL. À titre d'exemple, Yetkin et ses collègues ont étudié des TCL que l'on pourrait considérer comme moins atteints (MMSE moyen de 28) et ont trouvé des hyperactivations lors d'une tâche impliquant les fonctions exécutives (Yetkin, Rosenberg, Weiner, Purdy, & Cullum, 2005) tandis que Dannhauser et ses collaborateurs ont étudié des TCL plus atteints (MMSE moyen de 24) et ont plutôt observé des hypoactivations. Il serait ainsi intéressant de faire une méta-analyse de la littérature en séparant les études ayant des TCL plus atteints et moins atteints. Si le nombre d'études le permet, il serait aussi intéressant de prendre en considération le type de processus cognitif impliqué dans les tâches, étant donné que nous avons montré que cela influence la possibilité de mécanismes compensatoires.

Bien que les études de cette thèse aient répondu à nos questions initiales, plusieurs nouvelles interrogations en découlent. Premièrement, il serait intéressant de suivre ces TCL durant quelques années et de voir si une augmentation de la sévérité induit une transition de l'hyperactivation vers l'hypoactivation chez ces sujets et s'il y a corrélation avec une baisse des performances lors de l'exécution de la tâche. En plus

d'effectuer des contrastes entre les conditions et entre les groupes comme nous avons fait dans nos études, il serait enrichissant d'avoir aussi recours à des analyses de connectivité fonctionnelle. Ce type d'analyse nous permettrait de mieux identifier et départager les réseaux qui sont impliqués dans la tâche de ceux dits « alternatifs » qui servent aux mécanismes compensatoires. Jusqu'à présent, une seule étude a utilisé des analyses de connectivité fonctionnelle chez les TCL (Celone et al., 2006) et une seule les a utilisées chez les patients MA (Grady, Furey, Pietrini, Horwitz, & Rapoport, 2001) et elles ont toutes deux observé une altération des corrélations entre les structures impliquées dans la tâche. Il serait toutefois important de mieux comprendre l'impact de ce changement des connectivités sur les mécanismes compensatoires.

Il serait aussi intéressant d'étudier comment la sévérité de la maladie affecte le mode par défaut des sujets TCL, c'est-à-dire leur niveau de base d'activation lorsqu'ils ne font aucune tâche (donc au repos) (Raichle et al., 2001). En effet, il a été montré que ce mode par défaut est altéré chez les patients MA (Greicius, Srivastava, Reiss, & Menon, 2004) et il serait pertinent d'essayer d'identifier à quel moment de la maladie ces changements arrivent.

En sommes, les études de cette thèse ont permis d'identifier une interaction entre le niveau de sévérité des personnes TCL, le type de processus cognitif impliqué dans la tâche et le niveau d'activation observé comparativement aux sujets contrôles. Les résultats montrent une progression durant la phase TCL: les premiers stades sont caractérisés par la présence d'hyperactivations et de mécanismes compensatoires pour plusieurs processus cognitifs (encodage, recollection, manipulation de l'information et

attention divisée) tandis que les stades plus avancés sont caractérisés par des hypoactivations et par une dégradation des mécanismes compensatoires pour la plupart des processus cognitifs, sauf ceux connus pour être préservés plus longtemps dans la MA (familiarité et possiblement attention divisée). Ces données ont plusieurs implications cliniques et fondamentales et suggèrent que l'imagerie par résonance magnétique fonctionnelle pourrait être utilisée comme marqueur cérébral des effets d'intervention cognitive ou pharmacologique. En effet, ces résultats nous permettent de faire des prédictions sur la manière dont un traitement devrait moduler l'activation cérébrale chez les TCL. Il sera donc intéressant de vérifier si les traitements actuels ou futurs sont ou seront capables de contrer cette dégradation des mécanismes compensatoires et de ramener de l'hyperactivation chez des personnes TCL plus atteints.

Références pour introduction et discussion générale

Almkvist, O., Fratiglioni, L., Aguero-Torres, H., Viitanen, M., & Backman, L. (1999). Cognitive support at episodic encoding and retrieval: similar patterns of utilization in community-based samples of Alzheimer's disease and vascular dementia patients. *J Clin Exp Neuropsychol, 21*(6), 816-830.

American Psychiatric Association. (2000). *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (4th ed.): American Psychiatric Publishing, Inc.

Amieva, H., Lafont, S., Auriacombe, S., Le Carret, N., Dartigues, J. F., Orgogozo, J. M., et al. (2002). Inhibitory breakdown and dementia of the Alzheimer type: a general phenomenon? *J Clin Exp Neuropsychol, 24*(4), 503-516.

Anderson, N. D., Ebert, P. L., Jennings, J. M., Grady, C. L., Cabeza, R., & Graham, S. J. (2008). Recollection- and familiarity-based memory in healthy aging and amnestic mild cognitive impairment. *Neuropsychology, 22*(2), 177-187.

Arnold, S. E., Hyman, B. T., Flory, J., Damasio, A. R., & Van Hoesen, G. W. (1991). The topographical and neuroanatomical distribution of neurofibrillary tangles and neuritic plaques in the cerebral cortex of patients with Alzheimer's disease. *Cereb Cortex, 1*(1), 103-116.

Backman, L., Andersson, J. L., Nyberg, L., Winblad, B., Nordberg, A., & Almkvist, O. (1999). Brain regions associated with episodic retrieval in normal aging and Alzheimer's disease. *Neurology, 52*(9), 1861-1870.

Baddeley, A. (1996). Exploring the Central Executive. *The Quarterly Journal of Experimental Psychology A, 49*(1), 5-28.

Banich, M. T. (1998). The missing link: the role of interhemispheric interaction in attentional processing. *Brain Cogn, 36*(2), 128-157.

Becker, J. T., Mintun, M. A., Aleva, K., Wiseman, M. B., Nichols, T., & DeKosky, S. T. (1996). Compensatory reallocation of brain resources supporting verbal episodic memory in Alzheimer's disease. *Neurology, 46*(3), 692-700.

Belanger, S., & Belleville, S. (2009). Semantic inhibition impairment in mild cognitive impairment: a distinctive feature of upcoming cognitive decline? *Neuropsychology, 23*(5), 592-606.

Belanger, S., Belleville, S., & Gauthier, S. (2010). Inhibition impairments in Alzheimer's disease, mild cognitive impairment and healthy aging: effect of congruency proportion in a Stroop task. *Neuropsychologia, 48*(2), 581-590.

Belleville, S., Bherer, L., Lepage, E., Chertkow, H., & Gauthier, S. (2008). Task switching capacities in persons with Alzheimer's disease and mild cognitive impairment. *Neuropsychologia, 46*(8), 2225-2233.

Belleville, S., Chertkow, H., & Gauthier, S. (2007). Working memory and control of attention in persons with Alzheimer's disease and mild cognitive impairment. *Neuropsychology, 21*(4), 458-469.

Belleville, S., Gilbert, B., Fontaine, F., Gagnon, L., Menard, E., & Gauthier, S. (2006). Improvement of episodic memory in persons with mild cognitive impairment and healthy older adults: evidence from a cognitive intervention program. *Dement Geriatr Cogn Disord, 22*(5-6), 486-499.

Belleville, S., Rouleau, N., & Van der Linden, M. (2006). Use of the Hayling task to measure inhibition of prepotent responses in normal aging and Alzheimer's disease. *Brain Cogn, 62*(2), 113-119.

Belleville, S., Rouleau, N., Van der Linden, M., & Collette, F. (2003). Effect of manipulation and irrelevant noise on working memory capacity of patients with Alzheimer's dementia. *Neuropsychology, 17*(1), 69-81.

Belleville, S., Clement, F., Mellah, S., Gilbert, B., Fontaine, F., & Gauthier, S. Training-related brain plasticity in subjects at risk of developing Alzheimer's disease. *Brain (sous presse)*.

Bherer, L., Belleville, S., & Hudon, C. (2004). [Executive function deficits in normal aging, Alzheimer's disease, and frontotemporal dementia]. *Psychol Neuropsychiatr Vieil, 2*(3), 181-189.

Braak, H., & Braak, E. (1991). Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol (Berl), 82*(4), 239-259.

Braak, H., & Braak, E. (1995). Staging of Alzheimer's disease-related neurofibrillary changes. *Neurobiol Aging, 16*(3), 271-278; discussion 278-284.

Cabeza, R. (2002). Hemispheric asymmetry reduction in older adults: the HAROLD model. *Psychol Aging, 17*(1), 85-100.

Cabeza, R., Anderson, N. D., Locantore, J. K., & McIntosh, A. R. (2002). Aging gracefully: Compensatory brain activity in high-performing older adults. *Neuroimage, 17*(3), 1394-1402.

Cabeza, R., & Nyberg, L. (2000). Imaging cognition II: An empirical review of 275 PET and fMRI studies. *J Cogn Neurosci, 12*(1), 1-47.

Celone, K. A., Calhoun, V. D., Dickerson, B. C., Atri, A., Chua, E. F., Miller, S. L., et al. (2006). Alterations in memory networks in mild cognitive impairment and Alzheimer's disease: an independent component analysis. *J Neurosci, 26*(40), 10222-10231.

Chen, E. E., & Small, S. L. (2007). Test-retest reliability in fMRI of language: group and task effects. *Brain Lang, 102*(2), 176-185.

Collie, A., & Maruff, P. (2000). The neuropsychology of preclinical Alzheimer's disease and mild cognitive impairment. *Neurosci Biobehav Rev, 24*(3), 365-374.

Collie, A., Maruff, P., & Currie, J. (2002). Behavioral characterization of mild cognitive impairment. *J Clin Exp Neuropsychol, 24*(6), 720-733.

Dannhauser, T. M., Shergill, S. S., Stevens, T., Lee, L., Seal, M., Walker, R. W., et al. (2008). An fMRI study of verbal episodic memory encoding in amnestic mild cognitive impairment. *Cortex, 44*(7), 869-880.

Dannhauser, T. M., Walker, Z., Stevens, T., Lee, L., Seal, M., & Shergill, S. S. (2005). The functional anatomy of divided attention in amnestic mild cognitive impairment. *Brain, 128*(Pt 6), 1418-1427.

De Jager, C., Blackwell, A. D., Budge, M. M., & Sahakian, B. J. (2005). Predicting cognitive decline in healthy older adults. *Am J Geriatr Psychiatry, 13*(8), 735-740.

Dickerson, B. C., Salat, D. H., Bates, J. F., Atiya, M., Killiany, R. J., Greve, D. N., et al. (2004). Medial temporal lobe function and structure in mild cognitive impairment. *Ann Neurol, 56*(1), 27-35.

Dickerson, B. C., Salat, D. H., Greve, D. N., Chua, E. F., Rand-Giovannetti, E., Rentz, D. M., et al. (2005). Increased hippocampal activation in mild cognitive impairment compared to normal aging and AD. *Neurology, 65*(3), 404-411.

Dudas, R. B., Clague, F., Thompson, S. A., Graham, K. S., & Hodges, J. R. (2005). Episodic and semantic memory in mild cognitive impairment. *Neuropsychologia, 43*(9), 1266-1276.

Edelman, G. M., & Gally, J. A. (2001). Degeneracy and complexity in biological systems. *Proc Natl Acad Sci U S A, 98*(24), 13763-13768.

Elgh, E., Larsson, A., Eriksson, S., & Nyberg, L. (2003). Altered prefrontal brain activity in persons at risk for Alzheimer's disease: an fMRI study. *Int Psychogeriatr, 15*(2), 121-133.

Feldman, H. H., & Jacova, C. (2005). Mild Cognitive Impairment. *Am J Geriatr Psychiatry, 13*(8), 645-655.

Fernandez, G., Specht, K., Weis, S., Tendolkar, I., Reuber, M., Fell, J., et al. (2003). Intrasubject reproducibility of presurgical language lateralization and mapping using fMRI. *Neurology, 60*(6), 969-975.

Fletcher, P. C., & Henson, R. N. (2001). Frontal lobes and human memory: insights from functional neuroimaging. *Brain, 124*(Pt 5), 849-881.

Friston, K. J., & Price, C. J. (2003). Degeneracy and redundancy in cognitive anatomy. *Trends Cogn Sci, 7*(4), 151-152.

Gauthier, S., Reisberg, B., Zaudig, M., Petersen, R. C., Ritchie, K., Broich, K., et al. (2006). Mild cognitive impairment. *Lancet, 367*(9518), 1262-1270.

Golby, A., Silverberg, G., Race, E., Gabrieli, S., O'Shea, J., Knierim, K., et al. (2005). Memory encoding in Alzheimer's disease: an fMRI study of explicit and implicit memory. *Brain, 128*(Pt 4), 773-787.

Grady, C. L., Furey, M. L., Pietrini, P., Horwitz, B., & Rapoport, S. I. (2001). Altered brain functional connectivity and impaired short-term memory in Alzheimer's disease. *Brain, 124*(Pt 4), 739-756.

Grady, C. L., McIntosh, A. R., Beig, S., Keightley, M. L., Burian, H., & Black, S. E. (2003). Evidence from functional neuroimaging of a compensatory prefrontal network in Alzheimer's disease. *J Neurosci, 23*(3), 986-993.

Grady, C. L., McIntosh, A. R., & Craik, F. I. (2005). Task-related activity in prefrontal cortex and its relation to recognition memory performance in young and old adults. *Neuropsychologia, 43*(10), 1466-1481.

Greicius, M. D., Srivastava, G., Reiss, A. L., & Menon, V. (2004). Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. *Proc Natl Acad Sci U S A, 101*(13), 4637-4642.

Gron, G., Bittner, D., Schmitz, B., Wunderlich, A. P., & Riepe, M. W. (2002). Subjective memory complaints: objective neural markers in patients with Alzheimer's disease and major depressive disorder. *Ann Neurol, 51*(4), 491-498.

Gron, G., & Riepe, M. W. (2004). Neural basis for the cognitive continuum in episodic memory from health to Alzheimer disease. *Am J Geriatr Psychiatry, 12*(6), 648-652.

Kapur, S., Tulving, E., Cabeza, R., McIntosh, A. R., Houle, S., & Craik, F. I. (1996). The neural correlates of intentional learning of verbal materials: a PET study in humans. *Brain Res Cogn Brain Res, 4*(4), 243-249.

Kemppainen, N. M., Aalto, S., Wilson, I. A., Nagren, K., Helin, S., Bruck, A., et al. (2007). PET amyloid ligand [11C]PIB uptake is increased in mild cognitive impairment. *Neurology, 68*(19), 1603-1606.

Klunk, W. E., Engler, H., Nordberg, A., Wang, Y., Blomqvist, G., Holt, D. P., et al. (2004). Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Ann Neurol, 55*(3), 306-319.

Kurland, J., Naeser, M. A., Baker, E. H., Doron, K., Martin, P. I., Seekins, H. E., et al. (2004). Test-retest reliability of fMRI during nonverbal semantic decisions in moderate-severe nonfluent aphasia patients. *Behav Neurol, 15*(3-4), 87-97.

Hamalainen, A., Pihlajamaki, M., Tanila, H., Hanninen, T., Niskanen, E., Tervo, S., et al. (2007). Increased fMRI responses during encoding in mild cognitive impairment. *Neurobiol Aging, 28*(12), 1889-1903.

Heun, R., Freymann, K., Erb, M., Leube, D. T., Jessen, F., Kircher, T. T., et al. (2007). Mild cognitive impairment (MCI) and actual retrieval performance affect cerebral activation in the elderly. *Neurobiol Aging, 28*(3), 404-413.

Hudon, C., Belleville, S., & Gauthier, S. (2009). The assessment of recognition memory using the Remember/Know procedure in amnestic mild cognitive impairment and probable Alzheimer's disease. *Brain Cogn, 70*(1), 171-179.

Johannsen, P., Jakobsen, J., Bruhn, P., & Gjedde, A. (1999). Cortical responses to sustained and divided attention in Alzheimer's disease. *Neuroimage, 10*(3 Pt 1), 269-281.

Johnson, S. C., Schmitz, T. W., Moritz, C. H., Meyerand, M. E., Rowley, H. A., Alexander, A. L., et al. (2006). Activation of brain regions vulnerable to Alzheimer's disease: The effect of mild cognitive impairment. *Neurobiol Aging, 27*(11), 1604-1612.

Kalpouzos, G., Eustache, F., de la Sayette, V., Viader, F., Chetelat, G., & Desgranges, B. (2005). Working memory and FDG-PET dissociate early and late onset Alzheimer disease patients. *J Neurol, 252*(5), 548-558.

Kessler, J., Herholz, K., Grond, M., & Heiss, W. D. (1991). Impaired metabolic activation in Alzheimer's disease: a PET study during continuous visual recognition. *Neuropsychologia, 29*(3), 229-243.

Kircher, T., Weis, S., Freymann, K., Erb, M., Jessen, F., Grodd, W., et al. (2007). Hippocampal activation in MCI patients is necessary for successful memory encoding. *J Neurol Neurosurg Psychiatry, 78*(8), 812-818.

Lambon Ralph, M. A., Patterson, K., Graham, N., Dawson, K., & Hodges, J. R. (2003). Homogeneity and heterogeneity in mild cognitive impairment and Alzheimer's disease: a cross-sectional and longitudinal study of 55 cases. *Brain, 126*(Pt 11), 2350-2362.

Li, S.-C., & Lindenberger, U. (1999). Cross-level unification: A computational exploration of the link between deterioration of neurotransmitter systems dedifferentiation of cognitive abilities in old age. In E. L.-G. Nilsson and H. J. Markowitsch (Ed.), *Cognitive Neuroscience of Memory* (pp. 103–146.). Seattle: Hogrefe & Huber.

Logan, J. M., Sanders, A. L., Snyder, A. Z., Morris, J. C., & Buckner, R. L. (2002). Under-recruitment and nonselective recruitment: dissociable neural mechanisms associated with aging. *Neuron, 33*(5), 827-840.

Machulda, M. M., Ward, H. A., Borowski, B., Gunter, J. L., Cha, R. H., O'Brien, P. C., et al. (2003). Comparison of memory fMRI response among normal, MCI, and Alzheimer's patients. *Neurology, 61*(4), 500-506.

Mandzia, J., Black, S., Grady, C., McAndrews, M. P., & Graham, S. (2002). Encoding and retrieval in aging and memory loss, a fMRI study. *Brain Cogn, 49*(2), 225-228.

Mandzia, J. L., McAndrews, M. P., Grady, C. L., Graham, S. J., & Black, S. E. (2007). Neural correlates of incidental memory in mild cognitive impairment: An fMRI study. *Neurobiol Aging, doi:10.1016/j.neurobiolaging.2007.08.024*.

Manoach, D. S., Halpern, E. F., Kramer, T. S., Chang, Y., Goff, D. C., Rauch, S. L., et al. (2001). Test-retest reliability of a functional MRI working memory paradigm in normal and schizophrenic subjects. *Am J Psychiatry, 158*(6), 955-958.

Mattis, S. (1976). Mental status examination for organic mental syndrome in the elderly patient. In L. Bellak & T. B. Karasu (Eds.), *Geriatric Psychiatry* (pp. 77–121). New York: Grune & Stratton.

McDowell, I., Hill, G., Lindsay, J., Helliwell, B., Costa, L., & Beattie, B. L. (1994). Canadian study of health and aging: study methods and prevalence of dementia. *CMAJ, 150*(6), 899-913.

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology, 34*(7), 939-944.

Mebane-Sims, I. (2009). 2009 Alzheimer's disease facts and figures. *Alzheimers Dement, 5*(3), 234-270.

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex "Frontal Lobe" tasks: a latent variable analysis. *Cognit Psychol, 41*(1), 49-100.

Moulin, C. J., James, N., Freeman, J. E., & Jones, R. W. (2004). Deficient acquisition and consolidation: intertrial free recall performance in Alzheimer's disease and mild cognitive impairment. *J Clin Exp Neuropsychol, 26*(1), 1-10.

Nordahl, C. W., Ranganath, C., Yonelinas, A. P., DeCarli, C., Reed, B. R., & Jagust, W. J. (2005). Different mechanisms of episodic memory failure in mild cognitive impairment. *Neuropsychologia, 43*(11), 1688-1697.

Okonkwo, O. C., Wadley, V. G., Ball, K., Vance, D. E., & Crowe, M. (2008). Dissociations in Visual Attention Deficits among Persons with Mild Cognitive Impairment. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn, 15*(4), 492-505.

Pariente, J., Cole, S., Henson, R., Clare, L., Kennedy, A., Rossor, M., et al. (2005). Alzheimer's patients engage an alternative network during a memory task. *Ann Neurol, 58*(6), 870-879.

Parra, M. A., Abrahams, S., Fabi, K., Logie, R., Luzzi, S., & Della Sala, S. (2009). Short-term memory binding deficits in Alzheimer's disease. *Brain, 132*(Pt 4), 1057-1066.

Pereira, F. S., Yassuda, M. S., Oliveira, A. M., & Forlenza, O. V. (2008). Executive dysfunction correlates with impaired functional status in older adults with varying degrees of cognitive impairment. *Int Psychogeriatr*, 1-12.

Perri, R., Carlesimo, G. A., Serra, L., & Caltagirone, C. (2005). Characterization of memory profile in subjects with amnestic mild cognitive impairment. *J Clin Exp Neuropsychol, 27*(8), 1033-1055.

Perri, R., Serra, L., Carlesimo, G. A., & Caltagirone, C. (2007). Amnestic mild cognitive impairment: difference of memory profile in subjects who converted or did not convert to Alzheimer's disease. *Neuropsychology, 21*(5), 549-558.

Petersen, R. C., Doody, R., Kurz, A., Mohs, R. C., Morris, J. C., Rabins, P. V., et al. (2001). Current concepts in mild cognitive impairment. *Arch Neurol, 58*(12), 1985-1992.

Petersen, R. C., Smith, G. E., Waring, S. C., Ivnik, R. J., Tangalos, E. G., & Kokmen, E. (1999). Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol, 56*(3), 303-308.

Petersen, R. C., Thomas, R. G., Grundman, M., Bennett, D., Doody, R., Ferris, S., et al. (2005). Vitamin E and donepezil for the treatment of mild cognitive impairment. *N Engl J Med, 352*(23), 2379-2388.

Poldrack, R. A., Wagner, A. D., Prull, M. W., Desmond, J. E., Glover, G. H., & Gabrieli, J. D. (1999). Functional specialization for semantic and phonological processing in the left inferior prefrontal cortex. *Neuroimage, 10*(1), 15-35.

Price, C. J., & Friston, K. J. (2002). Degeneracy and cognitive anatomy. *Trends Cogn Sci, 6*(10), 416-421.

Prvulovic, D., Van de Ven, V., Sack, A. T., Maurer, K., & Linden, D. E. (2005). Functional activation imaging in aging and dementia. *Psychiatry Res, 140*(2), 97-113.

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proc Natl Acad Sci U S A, 98*(2), 676-682.

Ranganath, C., Johnson, M. K., & D'Esposito, M. (2000). Left anterior prefrontal activation increases with demands to recall specific perceptual information. *J Neurosci, 20*(22), RC108.

Ranganath, C., Cohen, M. X., & Brozinsky, C. J. (2005). Working memory maintenance contributes to long-term memory formation: neural and behavioral evidence. *J Cogn Neurosci, 17*(7), 994-1010.

Rapoport, S. I., & Grady, C. L. (1993). Parametric in vivo brain imaging during activation to examine pathological mechanisms of functional failure in Alzheimer disease. *Int J Neurosci, 70*(1-2), 39-56.

Remy, F., Mirrashed, F., Campbell, B., & Richter, W. (2005). Verbal episodic memory impairment in Alzheimer's disease: a combined structural and functional MRI study. *Neuroimage, 25*(1), 253-266.

Ries, M. L., Schmitz, T. W., Kawahara, T. N., Torgerson, B. M., Trivedi, M. A., & Johnson, S. C. (2005). Task-dependent posterior cingulate activation in mild cognitive impairment. *Neuroimage, 29*(2), 485-492.

Rombouts, S. A., Barkhof, F., Veltman, D. J., Machielsen, W. C., Witter, M. P., Bierlaagh, M. A., et al. (2000). Functional MR imaging in Alzheimer's disease during memory encoding. *AJNR Am J Neuroradiol, 21*(10), 1869-1875.

Rowe, C. C., Ng, S., Ackermann, U., Gong, S. J., Pike, K., Savage, G., et al. (2007). Imaging beta-amyloid burden in aging and dementia. *Neurology, 68*(20), 1718-1725.

Royall, D. R., Palmer, R., Chiodo, L. K., & Polk, M. J. (2005). Executive control mediates memory's association with change in instrumental activities of daily living: the Freedom House Study. *J Am Geriatr Soc, 53*(1), 11-17.

Sahakian, B. J., Morris, R. G., Evenden, J. L., Heald, A., Levy, R., Philpot, M., et al. (1988). A comparative study of visuospatial memory and learning in Alzheimer-type dementia and Parkinson's disease. *Brain, 111 (Pt 3)*, 695-718.

Schroder, J., Buchsbaum, M. S., Shihabuddin, L., Tang, C., Wei, T. C., Spiegel-Cohen, J., et al. (2001). Patterns of cortical activity and memory performance in Alzheimer's disease. *Biol Psychiatry, 49*(5), 426-436.

Small, S. A., Perera, G. M., DeLaPaz, R., Mayeux, R., & Stern, Y. (1999). Differential regional dysfunction of the hippocampal formation among elderly with memory decline and Alzheimer's disease. *Ann Neurol, 45*(4), 466-472.

Sperling, R. A., Bates, J. F., Chua, E. F., Cocchiarella, A. J., Rentz, D. M., Rosen, B. R., et al. (2003). fMRI studies of associative encoding in young and elderly controls and mild Alzheimer's disease. *J Neurol Neurosurg Psychiatry, 74*(1), 44-50.

Starr, J. M., Loeffler, B., Abousleiman, Y., Simonotto, E., Marshall, I., Goddard, N., et al. (2005). Episodic and semantic memory tasks activate different brain regions in Alzheimer disease. *Neurology, 65*(2), 266-269.

Swainson, R., Hodges, J. R., Galton, C. J., Semple, J., Michael, A., Dunn, B. D., et al. (2001). Early detection and differential diagnosis of Alzheimer's disease and depression with neuropsychological tasks. *Dement Geriatr Cogn Disord, 12*(4), 265-280.

Traykov, L., Rigaud, A. S., Cesaro, P., & Boller, F. (2007). [Neuropsychological impairment in the early Alzheimer's disease]. *Encephale, 33*(3 Pt 1), 310-316.

Tulving, E. (2004). [Episodic memory: from mind to brain]. *Rev Neurol (Paris), 160*(4 Pt 2), S9-23.

Wagner, A. D., Schacter, D. L., Rotte, M., Koutstaal, W., Maril, A., Dale, A. M., et al. (1998). Building memories: remembering and forgetting of verbal experiences as predicted by brain activity. *Science, 281*(5380), 1188-1191.

Wermke, M., Sorg, C., Wohlschlager, A. M., & Drzezga, A. (2008). A new integrative model of cerebral activation, deactivation and default mode function in Alzheimer's disease. *Eur J Nucl Med Mol Imaging, 35 Suppl 1*, S12-24.

Westerberg, C. E., Paller, K. A., Weintraub, S., Mesulam, M. M., Holdstock, J. S., Mayes, A. R., et al. (2006). When memory does not fail: familiarity-based recognition in mild cognitive impairment and Alzheimer's disease. *Neuropsychology, 20*(2), 193-205.

Winblad, B., Palmer, K., Kivipelto, M., Jelic, V., Fratiglioni, L., Wahlund, L. O., et al. (2004). Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *J Intern Med, 256*(3), 240-246.

Wolk, D. A., Signoff, E. D., & Dekosky, S. T. (2008). Recollection and familiarity in amnestic mild cognitive impairment: a global decline in recognition memory. *Neuropsychologia, 46*(7), 1965-1978.

Woodard, J. L., Grafton, S. T., Votaw, J. R., Green, R. C., Dobraski, M. E., & Hoffman, J. M. (1998). Compensatory recruitment of neural resources during overt rehearsal of word lists in Alzheimer's disease. *Neuropsychology, 12*(4), 491-504.

Yetkin, F. Z., Rosenberg, R. N., Weiner, M. F., Purdy, P. D., & Cullum, C. M. (2005). FMRI of working memory in patients with mild cognitive impairment and probable Alzheimer's disease. *Eur Radiol*.

ANNEXE I

Article n° 6

Cognitive complaint in mild cognitive impairment and Alzheimer's disease

Francis Clément, Sylvie Belleville & Serge Gauthier

Journal of the International Neuropsychological Society 2008; 14(2): 222-232.

Abstract

Whereas presence of a subjective memory complaint is a central criteria for mild cognitive impairment (MCI), little work has been done to empirically measure its nature and severity. The Self-Evaluation Questionnaire (QAM) assessed memory complaints relative to 10 domains of concrete activities of daily life in 68 persons with MCI, 26 persons with Alzheimer's disease (AD) and 81 healthy older adults. In addition, a neuropsychological battery was administered to assess whether subjective complaints were linked to actual cognitive performance. The findings indicate that individuals with MCI report more memory complaints than controls for a range of specific materials/circumstances. MCI and AD individuals did not differ in their level of memory complaints. Correlational analyses indicated that a higher level of memory complaints relative to conversations and to movies and books were associated with a higher level of objective cognitive deficits in persons with MCI but not in AD. Furthermore, complaints increased in parallel with global cognitive deficits in MCI. These results suggest that MCI report more memory complaints than healthy older controls, but only in specific domains and circumstances and that anosognosia is more characteristic of the demented than of the MCI phase of Alzheimer's disease.

Mesh or key words: memory, cognition, neuropsychology, dementia, amnesia, neuropsychological tests

Introduction

Mild cognitive impairment (MCI) has been identified as a risk factor for the development of AD as it has been shown that a large proportion of persons who meet the clinical criteria for MCI will progress to dementia (Gauthier et al., 2006). Typically, the criteria for MCI include the presence of an objective cognitive deficit relative to normative values and the presence of a subjective complaint (Petersen et al., 1999). In addition to being central to the defining criteria for MCI, the subjective complaint is also used by clinicians to support further investigation when there is suspicion of cognitive decline. Surprisingly, very little is known about the nature and severity of the cognitive complaints that characterize MCI.

One major objective of the present research was to assess the specific domains of complaint in persons with MCI. It is now well established that individuals with MCI do not show general cognitive decline and that episodic memory is the cognitive domain for which they show the greatest impairments (Collie & Maruff, 2000; Nordahl et al., 2005; Perri et al., 2005; Petersen et al., 1999). Thus, it is expected that the reported cognitive problems of people with MCI relate to domains that require episodic memory. However, the majority of studies only examined a global level of memory complaints and none have looked at specific domains of complaints. Such a global assessment approach could lead to misleading interpretations of the level of complaint. For instance, when asking one general question about subjective memory evaluation, Jungwirth et al. (2004) found that the majority (94%) of memory-impaired subjects did not complain about their memory, whereas Lam et al. (2005) obtained the opposite finding with a short (five

questions) memory complaint questionnaire. This may result from the narrow set of questions or from the nature of the domains addressed by short questionnaires.

Another important objective in relation to complaints in MCI was to assess their actual predictive value of objective capacities. Previous findings are inconsistent regarding whether or not memory complaints are representative of the actual cognitive deficits in this population. Lam and collaborators (2005) found an association between memory complaint and cognitive test performances. Yet, other studies have found no association between self-reported memory complaint and objective memory deficits (Carr et al., 2000; Derouesne et al., 2004; Farias et al., 2005; Jungwirth et al., 2004). Again, the way in which memory complaints are measured is an issue. It is possible that relying on a comprehensive or focused assessment of the complaint affords a better fit with cognitive performance.

Finally, an important question to address relates to the changes that occur in the level and nature of complaint as individuals progress through the MCI phase, and from MCI to AD. First, it is well accepted that AD is characterized by anosognosia and that the level of anosognosia in AD increases with the severity of the disease (Kashiwa et al., 2005; Starkstein et al., 2006). This inverse relationship between complaint and cognition as the disease progresses is illustrated in Figure 1A. However, it is unclear how the cognitive complaint evolves from MCI to AD and within the MCI phase. While some studies have concluded that individuals with MCI and individuals with AD have a similar level of anosognosia (Vogel et al., 2005; Vogel et al., 2004), others have found that persons with MCI report more cognitive problems (Kalbe et al., 2005) or functional

difficulties (Farias et al., 2005) than what is reported by their informant, indicating an overestimation of their deficits. One possibility is that these differences are a function of the phase during which MCI participants were tested: the initial phase could be associated with a higher level of complaint, which would decrease as persons develop more severe deficits and anosognosia. This association would mimic the one found in AD and shown in Fig 1A. On the other hand, the complaint could increase along with the deficits during the MCI phase, as illustrated in Figure 1B, with anosognosia only appearing during the AD phase along with the emergence of executive impairment. Discrepancies could also relate to the domains for which persons with MCI are questioned. However, to our knowledge, no study has investigated the level and nature of the complaint within the MCI stage and as a function of the severity level of cognitive deficit.

In summary, the literature on the nature and level of complaint in MCI is sparse and the data are inconclusive. Several factors could explain the divergent findings found in the literature. Many studies investigated memory complaint with a limited set of questions (the number of questions often varying between 1 and 5) or used a large-scale tool to measure cognition (e.g., Mini-Mental State Examination (MMSE)). These are relevant factors because persons with MCI have mild cognitive decline, which may be obscured by the use of gross cognitive tasks. The modest cognitive impairment of MCI may result in more focused areas of difficulty, and thus, of complaints. For these reasons, more specific measures of the memory complaints that are specific to the MCI population are warranted. In addition, the complaint may change as MCI evolves toward AD, and severity has to be taken into account.

The goal of the present study was to investigate self-reported complaints related to cognition in everyday situations in normal elderly persons, persons with MCI, and persons with AD by taking into account the aforementioned factors. More importantly, we wanted to characterize the nature and severity of the cognitive complaint of MCI and AD persons and to determine if this complaint is linked with their actual memory deficits and with the severity of their overall cognitive decline. We used the Self-Evaluation Questionnaire (QAM; Van der Linden et al., 1989) to assess self-reported complaints. The advantage of this questionnaire is that it contains a large number of questions grouped in sections that reflect different cognitive deficits: episodic memory, working memory, prospective memory, general events, face processing, orientation in space and praxia. In addition, results from neuropsychological tests were used to assess how subjective complaint is associated with actual cognitive performance. We focused on episodic memory and executive functions as these are components that are impaired during the MCI phase (Belleville & Ménard, 2006; Hodges, 2006). The influence of depression on complaint was also measured. Psychoaffective symptoms could lead to an over-estimation of the cognitive difficulties in persons with MCI in light of recent studies showing higher levels of anxiety and depression in these individuals (Gabryelewicz et al., 2004; Hwang et al., 2004; Kumar et al., 2006; Lopez et al., 2005; Lyketsos et al., 2002). Finally, the impact of progression in the disease and the role of the severity of cognitive deficits in complaint were measured. This was achieved by comparing the complaint in persons with MCI to that expressed by persons with AD, and by comparing the complaint in MCI persons with high and low global cognitive functioning.

We hypothesized that people with MCI would report more memory complaints than healthy older adults on the sections of the QAM that are indices of episodic memory and that their level of complaint would be equivalent or even more important than that of AD patients because individuals with AD are known to exhibit a certain degree of anosognosia. We also hypothesized that there would be an association between complaint and formal deficit in MCI and that persons with MCI who exhibit more severe cognitive impairments would show more cognitive complaints. However, no association was expected between complaint level and formal cognitive deficits in AD. Overall, this would be consistent with anosognosia appearing during the AD phase.

Method

Participants

A total of 175 participants, 26 AD patients, 68 persons with MCI, and 81 healthy older adults participated in this study. Three persons with MCI and one healthy control did not complete the entire QAM questionnaire and were thus excluded from some of the analyses. Healthy older adults (22 males) were between 50 and 87 years of age (M = 68.6; SD = 8.2), and had a mean of 14.2 years of education (SD = 3.6). Persons with MCI (29 males) were between 52 and 84 years of age (M = 69.1; SD = 7.9), with an average of 13.9 years of education (SD = 4.3), and persons with AD (13 males) were 51 to 85 years of age (M = 74.5; SD = 7.7) and had an average of 12.1 years of education (SD = 5.0). French was the first language of all participants.

Participants with AD and MCI were recruited from memory clinics where they had received their diagnosis following assessment by an experienced clinical neurologist and following extensive neuropsychological testing (see Table 1). In addition, AD and MCI participants went through an extensive medical, neurological and neuroradiological examination to exclude the presence of any other significant systemic, neurological or psychiatric condition that could explain their cognitive difficulties.

Participants with MCI met the criteria proposed by Petersen et al (1999) for amnestic and non-amnestic types, single or multiple domains: 1) they consulted because they worried about their memory; 2) they performed at least 1.5 SD below the average level of persons of similar age and education on standardized memory tests (single domain amnestic MCI), on standardized memory and non-memory tests (multiple domain amnestic MCI), or on standardized non-memory tests (non-amnestic MCI); 3) they showed no global cognitive impairment on the basis of the MMSE; 4) nor any significant impact on daily functions as measured by the SMAF functional impairment scale and clinical interview. Sixteen participants with MCI met the criteria for single domain amnestic MCI, 49 met the criteria for multiple domain amnestic MCI, and 3 met the criteria for non-amnestic MCI. AD patients were diagnosed according to the NINCDS-ADRDA (McKhann et al., 1984), and DSM-IV criteria. The severity of their disease ranged from mild to moderate, on the basis of the neuropsychological and clinical assessments. Elderly controls were recruited from the community. Healthy older adults also completed the clinical and neuropsychological assessment to ensure that they did not suffer from cognitive deficits. The study was approved by the Institut Universitaire de Gériatrie de Montréal Human Ethics Committee.

Memory questionnaire

The Self-Evaluation Complaint Questionnaire (QAM; Van der Linden et al., 1989) is composed of 64 questions divided into ten sections representing different dimensions of concrete activities and situations of daily life. The ten sections are 1-Conversation, 2-Movies and Books, 3-Slips of Attention, 4-People, 5-Use of Objects, 6-Political and Social Events, 7-Places, 8-Actions to Perform, 9-Personal Events, 10-General. The sections cover a range of cognitive domains including episodic memory (1-Conversation; 2-Movies and Books), working memory (3-Slips of Attention), persons' knowledge (4-People), praxia (5-Use of Objects), knowledge about general events (6-Political and Social Events), orientation in space (7-Places), prospective memory (8-Actions to Perform), autobiographical memory (9-Personal Events) and the impact of environmental/personal factors on memory (10-General). Each section includes 2 to 14 questions. For each question, participants make a judgment on a 6-point scale (from never = 1 to always = 6) about the frequency with which they encounter difficulties in a particular situation. A single score per section is determined by averaging the responses on all questions within the section. A total score, corresponding to the average score across sections, is also computed to assess the overall level of complaint. Examples of questions for each section are shown in Table 2.

Global Cognitive Function

The Mini-Mental State Examination (MMSE; Folstein et al., 1975) and the Mattis dementia rating scale (MDRS; Mattis, 1976) were used to assess global functioning and dementia severity.

xxx

Functional and psychological assessment

The Functional Autonomy Measurement System (SMAF; Desrosiers et al., 1995) was used to measure functional autonomy. It is a 29-item scale that measures functional ability in five areas: activities of daily living, mobility, communication, mental functions and instrumental activities of daily living. A total disability score (on –87) was calculated for each subject. Depression was assessed using the short version (5-item) of the Geriatric Depression Scale (GDS; Yesavage, 1988).

Memory

Memory was evaluated with a cued and free word recall task (RL/RI-16; Buschke, 1984; Van der Linden et al., 2004) and with a text memory of the BEM (Signoret, 1991). The RL/RI-16 allows for an assessment of patients' memory capacities when effective processing is provided during the learning of 16 words. There are three trials, with free recall followed by cued recall. A delayed free and cued recall is done after a 20 min-delay. Text memory involves presentation of a short story followed by its immediate and delayed recall.

Executive functions

Executive functions were evaluated with the third plate of Stroop-Victoria where participants are asked to name color words printed in non-corresponding colors of ink (Regard, 1981) and with the copy of Rey's complex figure. The score on the copy of the Rey's complex figure measures copy planning and strategy.

Data analysis

Groups differences on socio-demographic factors were assessed with one–way analyses of variance (ANOVA) for the continuous variables age and education. Difference in gender composition was assessed with chi-square. In the case of significant Group differences, further analyses included the relevant variable as a covariate.

To assess Groups differences on the QAM, a one–way multiple analysis of variance (MANOVA) was done using Group (controls, MCI, AD) as a between-subject factor on the scores of the ten sections of the QAM. MANOVA is used in designs that have multiple dependent measures likely to be intercorrelated as is the case here. It forms a new dependant variable that is a linear combination of the measured dependant variables. It is thus a conservative test that reduces the likelihood of type 1 error (Tabachnick & Fidell, 2007). In the case of a significant group difference on the MANOVA, analysis of the location of the difference was done by performing individual ANOVAs on the individual scores for each section.

A correlationnal approach was used to test the relationship between subjective complaint on the QAM sections, depression and cognitive performance. First, in order to reduce the number of variables, control for type 1 error and increase signal-to-noise ratio, performance on the cognitive tests were grouped to create three composite scores: a memory composite score, a composite score for the executive domain and a severity composite. The cognitive tests were placed on the same scale by calculating individual Z-scores using the mean and SD of the control group as a reference. The memory composite score was obtained by averaging the Z-scores on the BEM delayed recall,

RL/RI-16 free recall Trial 3, and RL/RI-16 delayed free recall. The executive composite score was obtained by averaging Z-scores on Rey's complex figure (score) and Stroop-Victoria (number of errors: note that to keep higher Z-scores as indicating higher performance, Z-scores for number of errors were reversed). The severity composite score was obtained by averaging the Z-scores on the MMSE and MDRS. It should be noted that a low severity score indicates low MMSE and MDRS scores, and thus higher deficits of global cognitive function. Pearson's partial correlations were then computed between the QAM sections, the GDS and three composite scores. We used only those sections for which significant MCI/Control group differences were found to reduce the number of comparisons. In order to control for type 1 error, a conservative p value of 0.005 was used as significance threshold.

The effect of overall cognitive deficit was assessed by separating participants with MCI into two groups: one with a higher level of overall cognitive functioning and one with a lower level of overall cognitive functioning. This was done using a split-median on the MDRS scores. The cognitive complaints of those with the highest MDRS scores (n=32) were compared to the cognitive complaints of those with the lowest scores (n=33) using a one–way MANOVA with Group (high-MDRS and low-MDRS) as a between-subject factor on the ten sections of the QAM. The same procedure was used with AD patients.

Results

Sociodemographic data

To assess whether the groups differed on age, a one–way analysis of variance (ANOVA) with Group (controls, MCI, AD) as a between-subject factor was performed. The analysis indicated a main Group effect, $F(2,172) = 5.65$, $p < 0.01$. Post-hoc tests indicated that AD patients were significantly older than controls and MCI, $p < 0.01$ in both cases. However, patients with MCI did not differ from controls. The age difference between patients with AD and persons with MCI is not surprising because MCI is considered to be a pre-clinical phase of AD. To assess whether age differences could account for our findings and whether age should be statistically controlled, a correlation was performed between age and the total number of complaints for each group. Age was not found to be significantly correlated with the number of complaints for any of our groups, $r = -0.19$, $r = -0.04$, $r = -0.09$, for AD, MCI, and controls respectively. Thus, this factor was not taken into consideration in our future analyses.

A one-way ANOVA with Group (controls, MCI, AD) as a between-subject factor was also performed on education and indicated no Group differences, $F(2,172) = 2.56$, N.S. A chi square analysis revealed that groups differed in their gender composition (chi square = 6.2, $p < 0.05$). Therefore, gender was used as a covariate in all further analyses.

Validity of the QAM

To address the external validity of the QAM, the association between the QAM and the SMAF was assessed in healthy older adults, in MCI persons and in AD patients. The QAM is a well-validated scale that measures the level of reported difficulties with

complex activities of daily life (Desrosiers et al., 1995). A Pearson's partial correlation (controlling for gender) between the QAM total score and the score on the SMAF indicated a significant negative correlation between the two tests in healthy older adults, $r = -0.30$, $p < 0.01$, in persons with MCI, $r = -0.24$, $p < 0.05$, and in AD patients, $r = -0.45$, $p < 0.05$. In other words, a higher level of cognitive complaints on the QAM was associated with a lower score on the SMAF, and thus with a lower level of self-reported functional autonomy.

Groups differences on the QAM

Figure 2 displays the scores obtained by healthy older adults, persons with MCI and AD patients on each section of the QAM and their average scores. Inspection of Figure 2 indicates that persons with MCI and with AD reported more cognitive complaints than healthy controls. It also indicates heterogeneity across domains, as MCI persons and AD did not differ from healthy older adults on all sections of the QAM. This was confirmed by a one–way multiple analysis of covariance (MANCOVA) with Group (controls, MCI, AD) as a between-subject factor and gender as a covariate performed on the scores of the ten sections of the QAM. The MANCOVA indicated a significant main Group effect, $\Lambda = 0.77$, $F(20,316) = 2.18$, $p < 0.01$. ANOVAs indicated significant main Group effects on the following sections: Conversations, $F(2,167) = 12.25$, $p < 0.001$, Movies and Books, $F(2,167) = 7.88$, $p = 0.001$, Slips of Attention, $F(2,167) = 3.23$, $p < 0.05$, Political and Social Events, $F(2,167) = 3.06$, $p < 0.05$, Places, $F(2,167) = 8.96$, $p < 0.001$, Personal Events, $F(2,167) = 4.74$, $p = 0.01$, and General, $F(2,167) = 3.16$, $p < 0.05$. Tukey's post-hoc tests indicated that individuals with AD and MCI reported a higher level of complaint than controls on the Conversation section, $p < 0.01$ in both

groups, on the Movies and Books section, $p < 0.05$ and $p < 0.01$ for AD and MCI respectively, and on the Places section, $p < 0.01$ in both groups. In addition, persons with MCI had a higher level of complaint than controls on the Slips of Attention section, $p < 0.05$, Personal Events section, $p < 0.01$, and on General section, $p < 0.05$. No significant differences between persons with MCI and AD were found on any of the sections.

Correlational analyses

Correlations between cognitive tests and the QAM sections tested the relationship between complaint and cognitive deficits. The results obtained on the composite scores by patients with MCI and AD are shown in Table 3 (by definition, the average Z-score of control participants is 0).

To assess the relation between cognitive performance and the different domains of complaints, Pearson's partial correlations (controlling for gender) were computed between the three composite scores and the QAM sections for which significant MCI/Control group differences were obtained (1-Conversation, 2-Movies and Books, 3-Slips of Attention, 7-Places, 9-Personal Events, 10-General). We also correlated the GDS with those sections of the QAM to assess the association between depression and cognitive complaint. The correlations are shown in Table 4. In persons with MCI, a higher level of complaints about Conversations (section 1) was associated with a lower global cognitive performance, $r = -0.39$, $p < 0.005$. In addition, the complaints relative to Movies and Books (QAM section 2) were negatively correlated with the executive composite scores in persons with MCI, $r = -0.47$, $p < 0.005$ (Table 4). Also, the complaints of AD patients relative to Slips of Attention (section 3) was positively

correlated with the memory composite score: $r = 0.53$, $p < 0.005$. In healthy older adults, none of the domains of complaints correlated significantly with cognitive composites scores. Finally, in neither groups was depression associated with composite scores[5]

MCI with high and low global cognitive functioning

We assessed whether or not individuals with MCI who had more severe global cognitive decline would report more memory complaints than those with better cognitive abilities. We used the MDRS scores as a measure of global cognitive functioning as it yielded the variability necessary for the use of a split-median and is not curtailed by ceiling effects. Furthermore, the MDRS investigates a broad range of cognitive functions, and hence might be more sensitive to MCI's quite subtle cognitive impairments. A split-median on the MDRS distinguished participant with high and low global cognitive functioning. A one–way MANOVA with Group (high-MDRS and low-MDRS) as a between-subjects factor was then performed on the scores on the ten sections of the QAM. A main group effect for the MANOVA was found, $\Lambda = 0.67$, $F(10,53) = 2.62$, $p < 0.05$. A significant Group effect was found for the Conversations section, $F(1,62) = 5.99$, $p < 0.05$ and for Movies and Books, $F(1,62) = 4.31$, $p < 0.05$ (Figure 3). Therefore, persons with MCI who have lower global cognitive function on the MDRS report more memory problems related to conversations, and to movies and books, but not to other areas.

[5] Because of the lack of a correlation between cognition and depression, it was unnecessary to perform an ANCOVA with this factor in spite of the presence of a group difference on this factor (Lovell et al., 1987).

The same procedure was performed for the patients with AD patients. No main Group effect for the MANOVA was found.

Discussion

The general goal of this study was to make a comprehensive assessment of self-reported complaints related to everyday cognitive situations in persons with MCI relative to normal elderly and AD patients, relate those to objective deficits and assess the effect of global cognitive deficits. Prior to discussing our main findings, we would like to stress that a moderate (negative) association was found between the QAM total score obtained by healthy older adults, MCI persons, and AD patients and their scores on a well validated scale of functional autonomy. This confirms that a higher number of cognitive complaints was associated with poorer self-reported functional autonomy and thus provides some external validity for the QAM. Furthermore, none of our sections was correlated with the geriatric depression scale (GDS) in either groups, indicating that depression did not contribute to the data. These two preliminary findings are important as they indicate that the QAM reflects subjective self-assessment of cognitive impairment, but not a by-product of depressive symptoms.

A first objective of this study was to evaluate the level of complaints expressed by persons with MCI and AD on different domains of cognition. We found that complaints differed across domains. People with MCI report more memory problems related to Conversations (section 1), Movies and Books (section 2), Slips of Attention (section 3), Places (section 7), Personal Events (section 9), and on the General section (section 10). Most of these sections address problems that require encoding and

retrieving the spatiotemporal context of information, a memory process particularly impaired in the MCI population (Collie & Maruff, 2000; Nordahl et al., 2005; Petersen et al., 1999). Thus, as predicted, subjective complaints are consistent with our knowledge regarding the nature of memory deficits in MCI. The level of complaint of AD patients was significantly higher than healthy controls in a subset of the domains for which MCI persons expressed complaints: Conversations, Movies and Books, and Places.

The second objective of this study was to evaluate the association between subjective and objective cognitive abilities measured by composite scores. It was found that only some domains of memory complaints in individuals with MCI were linked to their actual cognitive deficits: Conversations (section 1) was related to the global cognitive score and Movies and Books' (section 2) was associated with the executive score. It indicates that a short complaint questionnaire that would include the questions which are part of those two sections (see Table 5 for the list of questions) may represent a good indicator of actual cognitive deficits. It is however important to note that none of the QAM sections were related to the memory composite score. Thus persons with MCI complaint of memory deficits and these complaints are related to their general cognitive deficits but not to their actual memory deficits. This lack of a relationship between the QAM subscales and the memory composite score is in line with a recent study that shows that people with MCI have metamemory difficulties and are therefore poor at predicting their memory performance (episodic feeling-of-knowing) (Perrotin et al., 2007). This may suggest that the complaint of persons with MCI is based on an assessment of their general cognitive difficulties and not on a precise assessment of their performance on memory.

We found no significant correlations between cognitive performance and the QAM subscales in healthy controls. This indicates that the relationship between cognition and memory complaint is specific to MCI. One possible reason for this lack of a correlation is that a large number of personal factors contributes to memory complaint in older adults without memory deficits. Possibly, it is only when a significant amount of memory change occurs – such as is the case in MCI - that this factor actually accounts for interindividual variations in the level of complaint. There was also a remarkable absence of correlation between subjective complaints on memory domains and objective memory performance in AD patients. This is consistent with the anosognosia typically reported in AD patients (Farias et al., 2005; Kalbe et al., 2005). Notably, however, the number of AD participants in this study was relatively small (N = 26) and more statistical power might be required to uncover an association between objective deficits and cognitive complaints in AD. Hence, these results need to be replicated with a larger sample.

One final goal was to investigate the differences in the level and nature of cognitive complaint as a function of the severity of cognitive impairment in MCI and AD. We are aware that the level of severity measured in a cross-sectional sample cannot be entirely amenable to progression in the disease. However, our hypothesis was that participants with more severe overall cognitive deficit were more likely to be more advanced along the MCI/AD continuum. On that basis, it was predicted that individuals with MCI who exhibited more severe cognitive impairments would show more cognitive complaints and that anosognosia would only be present in participants with AD. The results of this study partially confirm this hypothesis: MCI persons who had larger

cognitive deficits report more problems with Conversation and with Movies and Books than those with smaller cognitive deficits. In addition, there is a correlation between the composite score of severity and the level of complaint on Section 1 (Conversation). This supports an increase in the complaint that parallels the cognitive decline during the MCI phase. Our data also suggest that the complaint does not increase further as patients progress into the AD phase. This relation between complaint and deficit during the MCI/AD continuum is illustrated in Figure 1B.

We are aware of the limitations of this study. First, as mentioned above, our sample of AD patients was relatively small and we may have lacked some statistical power for this population. The fact that participants with AD and MCI were recruited from memory clinics can also be judged as a limitation. Specifically, our sample is biased toward persons who consulted the clinics themselves and are thus somehow more sensitive to their problems, at least on a general level. It would be interesting to extend our results to a community-based sample that would include people who did not consult for their memory problems. A related limitation arises from the apparent circularity of the studying of memory complaint in a diagnostic category that contains memory complaint as a criteria. However, circularity is reduced by the fact that our goal was to characterize the specific domains of complaint in MCI and to assess the relationship between cognitive complaint and actual deficits as well as its change as a function of overall disease severity, rather than just confirm the presence of a complaint. Again, extending our results to a community-based sample would protect against circularity. A third limitation is the cross-sectional design of the study, which does not permit us to attribute direct causation between our variables, and which limits the interpretation of our findings in terms of progression. These individuals with MCI, as well as the patients with

AD, are currently being followed-up, which might allow us to obtain more conclusive results in the future. Also, we did not give the QAM to informants. Notably, however, the format of the questionnaire is not easily amenable to a third-party because some questions are specific to mental states and may not be evaluated from an outside point-of-view.

Overall, the findings of our study indicate that individuals with MCI report more memory complaints than healthy older controls, but only in specific domains and circumstances. Within these specific domains of complaint, only two (reported memory difficulties for conversations, and for movies and books) were found to be good indicators of their objective cognitive deficits , to increase in parallel with global cognitive deficits in MCI and to reach a plateau once the individual has progressed to AD. The complaints related to these two domains appear more relevant and better indicators of global cognitive deficits than other memory domains probably because they place a high demand on episodic memory processes.

References

Albert, S. M., Michaels, K., Padilla, M., Pelton, G., Bell, K., Marder, K., Stern, Y., & Devanand, D. P. (1999). Functional significance of mild cognitive impairment in elderly patients without a dementia diagnosis. *Am J Geriatr Psychiatry, 7*(3), 213-220.

Belleville, S., & Ménard, M.-C. (2006). Neuropsychologie du trouble cognitif léger ou milg cognitive impairment. In C. Belin, A.-M. Ergis & O. Moreau (Eds.), *Actualités sur les démences: Aspects cliniques et neuropsychologiques* (pp. 613-629). Marseille: Solal.

Buschke, H. (1984). Cued recall in amnesia. *Journal of Clinical Neuropsychology, 6*, 433-440.

Carr, D. B., Gray, S., Baty, J., & Morris, J. C. (2000). The value of informant versus individual's complaints of memory impairment in early dementia. *Neurology, 55*(11), 1724-1726.

Collie, A., & Maruff, P. (2000). The neuropsychology of preclinical alzheimer's disease and mild cognitive impairment. *Neurosci Biobehav Rev, 24*(3), 365-374.

Derouesne, C., Rapin, J. R., & Lacomblez, L. (2004). Memory complaints in 200 subjects meeting the diagnostic criteria for age-associated memory impairment: Psychoaffective and cognitive correlates. *Psychol Neuropsychiatr Vieil, 2*(1), 67-74.

Desrosiers, J., Bravo, G., Hebert, R., & Dubuc, N. (1995). Reliability of the revised functional autonomy measurement system (smaf) for epidemiological research. *Age Ageing, 24*(5), 402-406.

Farias, S. T., Mungas, D., & Jagust, W. (2005). Degree of discrepancy between self and other-reported everyday functioning by cognitive status: Dementia, mild cognitive impairment, and healthy elders. *Int J Geriatr Psychiatry, 20*(9), 827-834.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). Mini-mental state: A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research, 12*(3), 189-198.

Gabryelewicz, T., Styczynska, M., Pfeffer, A., Wasiak, B., Barczak, A., Luczywek, E., Androsiuk, W., & Barcikowska, M. (2004). Prevalence of major and minor depression in elderly persons with mild cognitive impairment--madrs factor analysis. *Int J Geriatr Psychiatry, 19*(12), 1168-1172.

Gauthier, S., Reisberg, B., Zaudig, M., Petersen, R. C., Ritchie, K., Broich, K., Belleville, S., Brodaty, H., Bennett, D., Chertkow, H., Cummings, J. L., de Leon, M., Feldman, H., Ganguli, M., Hampel, H., Scheltens, P., Tierney, M. C., Whitehouse, P., & Winblad, B. (2006). Mild cognitive impairment. *Lancet, 367*(9518), 1262-1270.

Hodges, J. R. (2006). Alzheimer's centennial legacy: Origins, landmarks and the current status of knowledge concerning cognitive aspects. *Brain, 129*(Pt 11), 2811-2822.

Hwang, T. J., Masterman, D. L., Ortiz, F., Fairbanks, L. A., & Cummings, J. L. (2004). Mild cognitive impairment is associated with characteristic neuropsychiatric symptoms. *Alzheimer Dis Assoc Disord, 18*(1), 17-21.

Jungwirth, S., Fischer, P., Weissgram, S., Kirchmeyr, W., Bauer, P., & Tragl, K. H. (2004). Subjective memory complaints and objective memory impairment in the vienna-transdanube aging community. *J Am Geriatr Soc, 52*(2), 263-268.

Kalbe, E., Salmon, E., Perani, D., Holthoff, V., Sorbi, S., Elsner, A., Weisenbach, S., Brand, M., Lenz, O., Kessler, J., Luedecke, S., Ortelli, P., & Herholz, K. (2005). Anosognosia in very mild alzheimer's disease but not in mild cognitive impairment. *Dement Geriatr Cogn Disord, 19*(5-6), 349-356.

Kashiwa, Y., Kitabayashi, Y., Narumoto, J., Nakamura, K., Ueda, H., & Fukui, K. (2005). Anosognosia in alzheimer's disease: Association with patient characteristics, psychiatric symptoms and cognitive deficits. *Psychiatry Clin Neurosci, 59*(6), 697-704.

Kumar, R., Parslow, R. A., Jorm, A. F., Rosenman, S. J., Maller, J., Meslin, C., Anstey, K. J., Christensen, H., & Sachdev, P. S. (2006). Clinical and neuroimaging correlates of mild cognitive impairment in a middle-aged community sample: The personality and total health through life 60+ study. *Dement Geriatr Cogn Disord, 21*(1), 44-50.

Lam, L. C., Lui, V. W., Tam, C. W., & Chiu, H. F. (2005). Subjective memory complaints in chinese subjects with mild cognitive impairment and early alzheimer's disease. *Int J Geriatr Psychiatry, 20*(9), 876-882.

Lopez, O. L., Becker, J. T., & Sweet, R. A. (2005). Non-cognitive symptoms in mild cognitive impairment subjects. *Neurocase, 11*(1), 65-71.

Lovell, M., Franzen, M. D., & Golden, C. J. (1987). Statistical techniques in neuropsychology, iv: Analysis of covariance. *The international Journal of Clinical Neuropsychology, 9*, 49-55.

Lyketsos, C. G., Lopez, O., Jones, B., Fitzpatrick, A. L., Breitner, J., & DeKosky, S. (2002). Prevalence of neuropsychiatric symptoms in dementia and mild cognitive

impairment: Results from the cardiovascular health study. *Jama, 288*(12), 1475-1483.

Mattis, S. (1976). Mental status examination for organic mental syndrome in the elderly patient. In L. Bellak & T. B. Karasu (Eds.), *Geriatric psychiatry*. New York: Grune & Stratton.

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E. M. (1984). Clinical diagnosis of alzheimer's disease: Report of the nincds-adrda work group under the auspices of department of health and human services task force on alzheimer's disease. *Neurology, 34*(7), 939-944.

Nordahl, C. W., Ranganath, C., Yonelinas, A. P., DeCarli, C., Reed, B. R., & Jagust, W. J. (2005). Different mechanisms of episodic memory failure in mild cognitive impairment. *Neuropsychologia, 43*(11), 1688-1697.

Perri, R., Carlesimo, G. A., Serra, L., & Caltagirone, C. (2005). Characterization of memory profile in subjects with amnestic mild cognitive impairment. *J Clin Exp Neuropsychol, 27*(8), 1033-1055.

Perrotin, A., Belleville, S., & Isingrini, M. (2007). Metamemory monitoring in mild cognitive impairment: Evidence of a less accurate episodic feeling-of-knowing. *Neuropsychologia*, doi:10.1016/j.neuropsychologia.2007.05.003.

Petersen, R. C., Smith, G. E., Waring, S. C., Ivnik, R. J., Tangalos, E. G., & Kokmen, E. (1999). Mild cognitive impairment: Clinical characterization and outcome. *Arch Neurol, 56*(3), 303-308.

Regard, M. (1981). Cognitive rigidity and flexibility: A neuropsychological study: University of Victoria, Canada.

Signoret, J. L. (1991). *Batterie d'efficience mnésique bem 144*. Paris: Elsevier.

Starkstein, S. E., Jorge, R., Mizrahi, R., & Robinson, R. G. (2006). A diagnostic formulation for anosognosia in alzheimer's disease. *J Neurol Neurosurg Psychiatry, 77*(6), 719-725.

Tabachnick, B. G., & Fidell, L. S. (2007). *Using multivariate statistics* (Pearson Education ed.). Boston.

Van der Linden, M., Adam, S., Agniel, A., Baisset-Mouly, C., Bardet, F., Coyette, F., Desgranges, B., Deweer, B., Ergis, A. M., Gély-Nargeot, M. C., Grimomprez, L., Juillerat, A. C., Kalafat, M., Poitrenaud, J., Sellal, F., & Thomas-Antérion, C. (2004). *L'évaluation de troubles de la mémoire: Présentation de quatre tests de mémoire épisodique (avec étalonnage)*. Marseille: Solal.

Van der Linden, M., Wijns, C., Von Frenkell, R., Coyette, F., & Seron, X. (1989). *Un questionnaire d'auto-évaluation de la mémoire (qam)*. Bruxelles: Editest.

Vogel, A., Hasselbalch, S. G., Gade, A., Ziebell, M., & Waldemar, G. (2005). Cognitive and functional neuroimaging correlate for anosognosia in mild cognitive impairment and alzheimer's disease. *Int J Geriatr Psychiatry, 20*(3), 238-246.

Vogel, A., Stokholm, J., Gade, A., Andersen, B. B., Hejl, A. M., & Waldemar, G. (2004). Awareness of deficits in mild cognitive impairment and alzheimer's disease: Do mci patients have impaired insight? *Dement Geriatr Cogn Disord, 17*(3), 181-187.

Yesavage, J. A. (1988). Geriatric depression scale. *Psychopharmacological Bulletin, 24*, 709-711.

Acknowledgement

This work was supported by a National Research Award from the FRSQ to SB and by a grant from the CIHR to SB. FC was supported by a scholarship from the Fond Québécois de la Recherche sur la Nature et les Technologies (FQRNT). We thank Sara Bélanger for her suggestions and comments, Émilie Lepage for the neuropsychological evaluation of the participants and Janet Boseovski and Harold Gaboury for editorial assistance. The authors have reported no conflicts of interest.

Table 1.

Sociodemographic status and neuropsychological evaluation for the three groups. SD is in parenthesis.

	Controls n = 81	MCI n = 68	AD n = 26
Age	68.59 (8.20)	69.06 (7.89)	74.50 (7.75) **
Education	14.19 (3.56)	13.88 (4.34)	12.12 (4.97)
MDRS	140.64 (2.89)	136.12 (4.95)**	120.88 (10.42)**
MMSE	28.91 (0.92)	27.96 (1.76) **	23.77 (3.64) **
GDS (/5)	0.70 (0.89)	1.09 (1.18)	1.23 (1.34)
Coding	11.00 (2.67)	9.22 (2.61) **	7.00 (3.01) **
Benton Judgment of line orientation	23.94 (3.87)	22.69 (4.69)	19.62 (5.89) **
BEM Immediate recall	8.93 (1.72)	6.51 (2.24) **	2.75 (1.72) **
BEM Delayed recall	8.64 (1.79)	5.82 (2.40) **	1.46 (1.78) **
SMAF	-0.17 (0.44)	-0.76 (0.77)	-4.74 (6.36) **
Copy of Rey's Figure: time	217.09 (96.26)	268.72 (122.09)	367.08 (204.79)**
Copy of Rey's Figure: score	32.09 (3.90)	29.43 (5.37) **	24.54 (7.14) **
Stroop 3rd plate time	29.27 (8.44)	35.11 (12.22) *	51.29 (20.86) **
Stroop 3rd plate errors	1.16 (1.43)	2.79 (3.02) **	4.85 (4.70) **
RL/RI-16 3rd free recall	11.88 (2.05)	8.94 (3.35) **	2.88 (2.72) **
RL/RI-16 delayed free recall	12.56 (2.31)	9.83 (3.55) **	2.38 (3.09) **

Note. impairment relative to the controls at * $p < 0.05$; ** at $p < 0.01$

Table 2.

Examples of questions from each section of the QAM

Domains	Examples of questions
1- Conversation	Do you forget the content of a conversation that took place a few days before? Do you have difficulty following up on a conversation going on among many people because you forget what has just been said ?
2- Movies and Books	Do you have difficulty in remembering the story of a movie seen a few days before? Do you have difficulty in reading because you forget what you have just read, which obliges you to read the same text again ?
3- Slips of Attention	Do you forget to pick up personal objects when leaving a place? (e.g. Keys, hat, etc.). Do you sometimes enter a room to do something and forget what it was that you wanted to do?
4- People	Do you have difficulty in remembering the name of a person you have met recently and still meet from time to time? Do you have difficulty in recognizing famous people's faces?
5- Use of Objects	Do you have difficulty in remembering how to appropriately use an object? Do you have difficulty in learning how to use an object you have never used before ?
6- Political and Social Events	Do you have difficulty in remembering current events? Do you have difficulty in learning new knowledge (academic, professional, or other) ?

7- Places	Do you have difficulty in learning a new itinerary? Do you forget the name of a street that you know well?
8- Actions to Perform	Do you forget to perform an action you planned on doing? Do you forget meetings ?
9- Personal Events	Do you forget past personal events from a few days or weeks before? Do you hesitate to buy something because you are not sure if you already own it ?
10- General	Is it more difficult for you to learn something while in a noisy environment? Is it more difficult for you to learn something when you are tired ?

Table 3

Mean Z-scores (and standard deviations) obtained by persons with MCI and AD.

Scores	MCI	AD
	n = 71	n = 26
Severity	-1.33 (1.53) **	-6.29 (3.39) **
Memory	-1.43 (1.29) **	-4.34 (1.11) **
Executive Functions	-0.93 (1.36) **	-2.30 (2.13) **

Note. impairment relative to the controls at ** $p < 0.01$

Table 4

Correlations between QAM sections with GDS and scores of severity, memory and executive functions.

			Composite Scores		
		GDS	Severity	Memory	Executive Fcts
Conversation	MCI	0.14	-0.39 *	-0.31	-0.29
	AD	0.17	-0.21	0.16	-0.13
	CA	0.08	-0.15	-0.18	0.12
Movies and Books	MCI	0.05	-0.22	-0.27	-0.47*
	AD	0.09	-0.26	0.14	-0.47
	CA	0.06	-0.23	-0.26	0.09
Slips of Attention	MCI	0.13	0.08	0.05	-0.22
	AD	0.22	0.06	0.53 *	-0.25
	CA	0.22	-0.04	-0.09	0.08
Places	MCI	0.16	-0.02	-0.10	-0.11
	AD	0.12	-0.08	0.40	-0.23
	CA	0.17	-0.09	-0.13	0.02
Personal Events	MCI	0.08	-0.04	-0.09	-0.21
	AD	0.18	-0.12	0.32	-0.24
	CA	0.16	-0.09	-0.12	0.08
General	MCI	0.13	-0.16	-0.24	-0.23
	AD	0.08	-0.11	0.31	-0.29
	CA	0.04	-0.23	-0.13	0.10

Note. * $p < 0.005$

Table 5

Questions from sections Conversation and Movies and Books of the QAM

Domains	Questions
1- Conversation	Do you have difficulty in following up on a conversation going on with one person because you forget what has just been said ? Do you have difficulty in following up on a conversation going on among many people because you forget what has just been said ? During a conversation, do you repeat many times the same thing because you forgot that you have just said it ? Does it happen that you repeat something again and again because you forget that you have already said it a few hours or a few days before? Do you forget the content of a conversation that took place a few days before? Do you forget the content of a conversation that has just taken place?
2- Movies and books	Do you have difficulty in reading because you forget what you have just read, which obliges you to read the text again ? Do you have difficulty in remembering what you have read a few days before? Do you have difficulty in following a movie or a TV program because you forget what just happened? Do you have difficulty in remembering the story of a movie you have seen a few days before?

Figure Caption

Figure 1. Two possible models of the relationship between cognitive impairment and complaint in Alzheimer's Disease

Figure 2. Score obtained on the ten sections of the QAM by persons with MCI, AD patients and control participants. Note. * $p < 0.05$; ** $p < 0.01$

Figure 3. Score obtained on the ten sections of the QAM by individuals with MCI with high-MDRS scores and by individuals with MCI with low-MDRS scores. Note. * $p < 0.05$

Figure 1. Two possible models of the relationship between cognitive impairment and complaint in Alzheimer's Disease

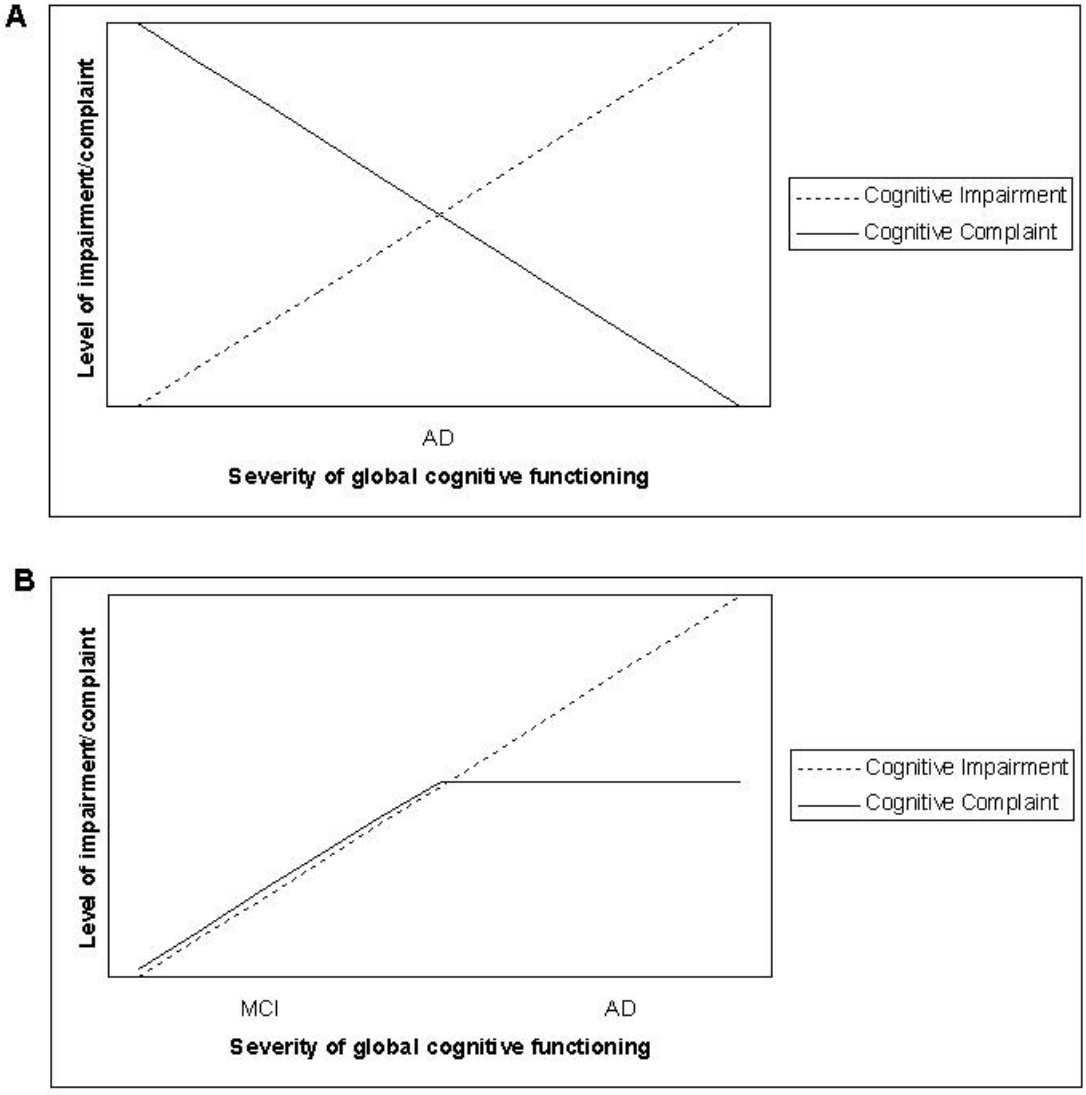


Figure 2. Score obtained on the ten sections of the QAM by persons with MCI, AD patients and control participants.

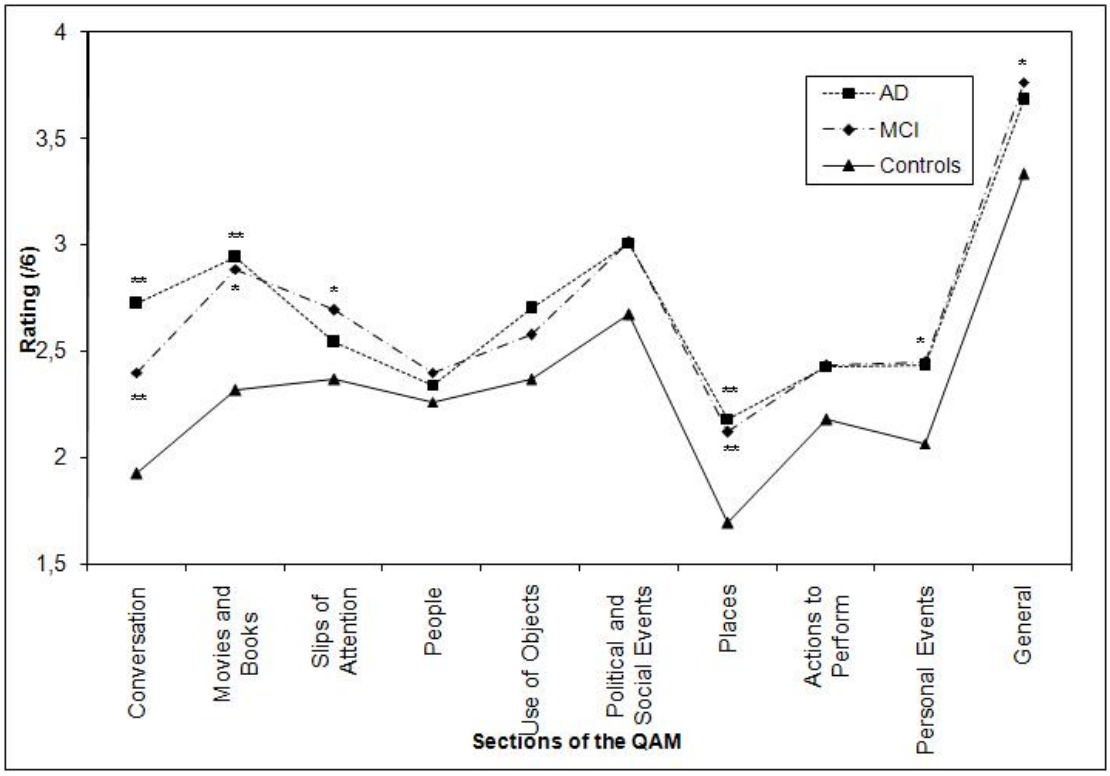
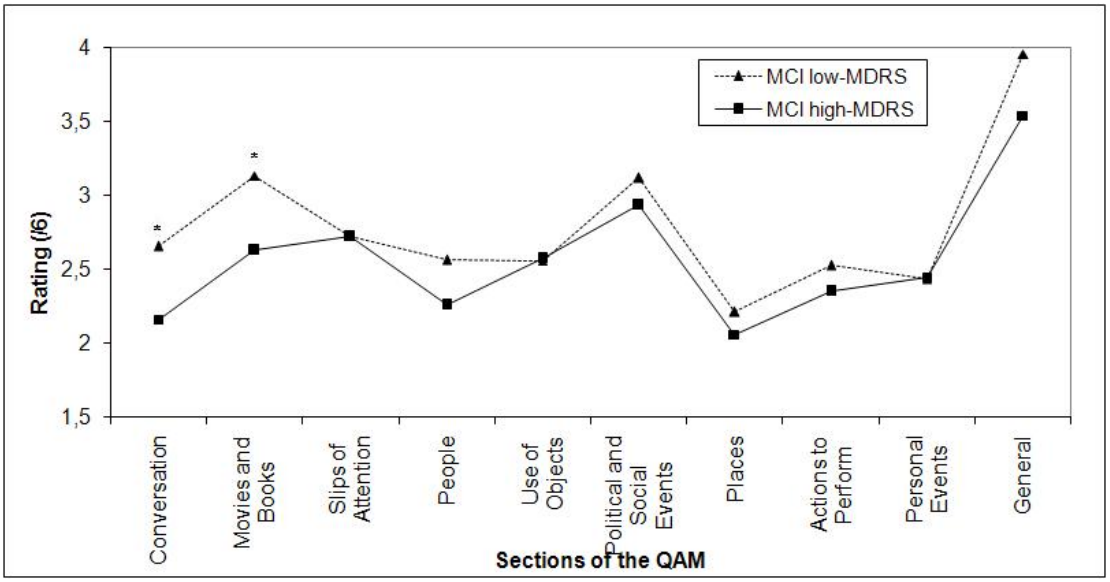


Figure 3. Score obtained on the ten sections of the QAM by individuals with MCI with high-MDRS scores and by individuals with MCI with low-MDRS scores.



ANNEXE II

Article n° 7

Personality and psychological health in persons with mild cognitive impairment

Francis Clément, Sylvie Belleville, Sara Bélanger & Véronique Chassé

Canadian Journal on Aging 2008; 28(2): 147-156

Abstract

An increasing number of studies have documented the cognitive profile of individuals with mild cognitive impairment (MCI), but few studies have investigated their psychological health and personality traits**,** as well as how these factors interact with cognition. In the present study, 27 healthy older adults and 30 persons with MCI completed questionnaires covering psychological health, morale, personality, self-efficacy and self-actualization. The results indicated that individuals with MCI are more depressed, anxious, hostile, and have lower morale than matched healthy older adults. Furthermore, our results show a positive association between the level of depression of MCI persons and the severity of their cognitive dysfunctions. In contrast, there were no group differences on measures of personality traits. Thus while psychological distress is present in persons with MCI, those individuals are not characterized by differences in personality traits relative to older adults experiencing no cognitive impairment.

Plusieurs études ont documenté le profil cognitif des individus avec un trouble cognitif léger (TCL ou MCI), mais très peu se sont intéressées à leur santé psychologique et leurs traits de personnalité, ainsi qu'aux interactions entre ces facteurs et la cognition. Dans cette étude, 27 personnes âgées saines et 30 personnes avec un TCL ont complété une évaluation neuropsychologique ainsi que des questionnaires portant sur la santé psychologique, bien-être, la personnalité, l'auto-efficacité et l'auto-actualisation. Les résultats indiquent que les individus avec un TCL sont plus déprimés, anxieux, hostiles et ont moins de bien-être que ce que rapporte un groupe de personnes âgées sans trouble de cognition. De plus, nos résultats montrent une association positive entre le niveau de dépression des personnes

TCL et la sévérité de leurs atteintes cognitives. En revanche, aucune différence n'est observée entre les groupes sur les échelles de personnalité. Ainsi, alors que la détresse psychologique est présente chez les personnes avec un TCL, ces personnes ne montrent pas de différence de traits de personnalité par rapport aux personnes âgées n'éprouvant pas de troubles cognitifs.

Keywords: Alzheimer's disease; depression; anxiety; cognition; neuropsychology

Introduction

Strong cognitive abilities are important in our ever-changing society, where attention, memory and executive functions are placed at a premium to keep up with the evolving technology and the constant influx of new information. Unfortunately, aging is often associated with a certain amount of decline in cognitive abilities, which can in some circumstances have maladaptive impacts and is often accompanied or exacerbated by psychological distress. This is likely to be the case for the 3-19 % of the elderly population who suffer from mild cognitive impairment (MCI). Individuals with MCI (Gauthier *et al.*, 2006; Petersen *et al.*, 2001; Petersen *et al.*, 1999) experience atypical cognitive changes and perform below expected norms based on their age and education on formal cognitive measures, yet fail to meet criteria for Alzheimer's disease (AD) (Petersen et al., 2001). Follow-up studies have shown that a large proportion of persons meeting criteria for MCI will eventually progress to dementia (Gauthier et al., 2006).

While the majority of studies have documented the cognitive profile of individuals with MCI, there has been few detailing psychological assessment of MCI. Yet recent studies indicate that MCI could be associated with a substantial burden on patients' lives as it diminishes well-being and creates concerns about changing family roles due to cognitive impairment (Frank *et al.*, 2006). Furthermore, it has been observed that depression is common in individuals with MCI (Gabryelewicz *et al.*, 2004; Kumar *et al.*, 2006), and that their mood disturbances, much like their cognitive capacities, are typically at an intermediate level between AD patients and healthy older adults (Li, Meyer, & Thornby, 2001; Lyketsos *et al.*, 2002), but can even be at the same level as AD patients (Hwang, Masterman, Ortiz, Fairbanks, & Cummings, 2004; Lopez, Becker, &

Sweet, 2005). In addition, depression is a risk factor for the development of MCI in older persons (Kumar et al., 2006; Lopez *et al.*, 2003) and there is also some indication that depression is a risk factor for progression to AD (Li et al., 2001; Modrego & Ferrandez, 2004 but see Copeland *et al.*, 2003; Robert *et al.*, 2006). These findings suggest that cognitive decline may be associated with psychological distress. However, factors other than depression, such as hostility and morale, are rarely assessed in MCI and consequently, little is known about their impact on personality changes; furthermore, the interaction between cognition and psychological distress is not well understood in persons with MCI.

Although virtually nothing is known about the complex relationship between personality, cognition, and psychological health in MCI, it is now known that in healthy aging the amount of psychological distress associated with the cognitive decline can be mediated to a certain extent by personality traits. For instance, a strong internal locus of control and a low level of neuroticism appear to be protective in older adults when experiencing impairments in general cognitive functioning, fluid intelligence, memory, or information processing speed (Van den Heuvel, Smits, Deeg, & Beekman, 1996). Along the same line, high neuroticism and low mastery predict the onset of depression (Steunenberg, Beekman, Deeg, & Kerkhof, 2006) in the elderly population. Interestingly, openness (intellectual curiosity, imagination, and a preference for variety and mental stimulation), extraversion (excitement-seeking and warmth), and neuroticism (nervousness, impulsivity, and moodiness) are positively correlated with a number of cognitive functions, including general ability, executive functions, memory, and fluid intelligence (Booth, Schinka, Brown, Mortimer, & Borenstein, 2006; Jorm *et al.*, 1993;

Meier, Perrig-Chiello, & Perrig, 2002 but see Jelicic *et al.*, 2003). In summary, there is some indication that personality traits can influence the psychological response to a decline in cognitive abilities in older adults, and that they are associated with cognitive functioning to a certain extent.

Personality seems to be quite stable in older adults, reaching a peak trait consistency of approximately .74 between the ages of 50 and 70 years (see Roberts & DelVecchio, 2000, for an extensive meta-analysis of 152 longitudinal studies). There is however ample evidence indicating that personality is altered by neurodegenerative disease that would lesion brain areas involved in complex emotional processing. Though the location of these regions is still controversial, some key regions of the prefrontal cortex (dorsolateral prefrontal cortex, anterior cingulate cortex and orbitofrontal cortex) and of the limbic structures (amygdala, hippocampus, and nucleus accumbens) have been found to be associated with temperament (Talassi, Cipriani, Bianchetti, & Trabucchi, 2007) and their dysfunction in AD (Arnold, Hyman, Flory, Damasio, & Van Hoesen, 1991; Braak & Braak, 1991) may result in personality changes. Accordingly, many studies have reported personality changes in patients with AD (Aitken, Simpson, & Burns, 1999; Jacomb & Jorm, 1996; Petry, Cummings, Hill, & Shapira, 1989; Talassi et al., 2007) and some have reported a positive correlation between the magnitude of these changes and cognitive impairment (Aitken et al., 1999; Talassi et al., 2007 but see Petry et al., 1989). Using a longitudinal design, Strauss & Pasupathi (1994) found that AD patients experienced an increase of neuroticism, a decrease in the level of extraversion, and a diminished level of conscientiousness over a one-year period. There is thus strong support to the notion that AD is accompanied by a gradual change in personality traits. In

contrast, only a few studies have investigated personality in prodromal AD while no studies have included persons with MCI. Meins and Dammast (2000) found that AD patients showed a lower premorbid level of neuroticism than Parkinson's disease (PD) patients but their study did not include a comparison with healthy older adults. Copeland and colleagues (2003) found that personality change in older adults with questionable dementia (CDR of 0.5) was a risk factor for converting to AD. The finding is thus inconsistent regarding the presence of personality changes in prodromal AD and nothing is known regarding MCI. Because many of those with MCI will develop dementia, personality traits can be expected to be altered in those individuals. In turn, many studies have reported that the prefrontal cortex is functional in MCI (Chetelat *et al.*, 2002; Pennanen *et al.*, 2005; Whitwell *et al.*, 2007), suggesting that personality or temperament may not be modified in this population.

The goal of the current study was to compare the psychological profile of individuals with MCI and healthy older adults by assessing personality traits (neuroticism, extraversion, self-efficacy, and self-actualization) and psychological health (depression, anxiety, hostility, and morale). In addition, we investigated the association between personality traits, psychological health and cognitive functions (general cognitive functioning, memory, perception, and executive functions). We hypothesized that persons with MCI would show more psychological distress than healthy older adults. Mood disturbances and morale would be particularly affected, as suggested by the reviewed literature, and mood disturbances were expected to be positively correlated with cognitive impairment in MCI. Whether MCI persons would differ from healthy controls on personality traits was unclear based on the published literature but

considering the lack of frontal dysfunction in this population, it was hypothesized that individuals with MCI would not experience personality changes/disturbances. Hence no correlation was expected between cognitive functions and personality traits in MCI. Lastly, we hypothesized that the way personality and psychological health influence each other would not differ in MCIs and healthy older adults.

Method

Participants

The current study included 57 older participants: 30 persons with MCI (14 males) and 27 education and age-matched healthy older (7 males) adults. Participants with MCI were recruited from memory clinics in the Montreal area. Healthy older adults were recruited from the same community[1], and thus from a similar socio-cultural background, through advertisements in newspapers or seniors clubs. Healthy older participants were matched to MCI participants on socio-demographic factors. The average age was 68.19 years (SD = 8.37) for the healthy older adults and 65.97 years (SD = 10.43) for individuals with MCI. Healthy older adults had a mean of 14.11 years of education (SD = 4.01) while persons with MCI had an average of 14.5 years of education (SD = 4.66).

MCI individuals went through an extensive medical, neurological and neuroradiological examination to exclude the presence of any other significant disease that could explain their cognitive difficulties. They were identified as MCI by experienced clinical neurologists or geriatricians and following extensive neuropsychological and clinical assessment. The clinical assessment included the Mini-

Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975), the Mattis Dementia Rating Scale (MDRS; Mattis, 1976), the Geriatric Depression Scale (GDS; Yesavage, 1988), the Hachinski scale to measure vascular risk (Hachinski, Iliff, Zilka, & et, 1975), the Self-Evaluation Questionnaire to measure memory complaint (QAM; Van der Linden et al., 1989), and the SMAF (Desrosiers, Bravo, Hebert, & Dubuc, 1995) to measure functional independence. We also used a section of the OARS Multidimensional functional assessment questionnaire to measure functional status (MFAQ; Fillenbaum & Smyer, 1981). The original OARS (Older Americans Resources and Services) instrument was used to measure the functional level of adults and elders according to five dimensions: social functioning, economical provisions, mental health, physical health and day-to-day activities. We used the physical health and social functioning sections, which have been validated in French.

The standardized neuropsychological battery measured memory (a cued and free word recall task, RL/RI-16, Van der Linden *et al.*, 2004), executive functions (Stroop-Victoria; Regard, 1981), and visuospatial processing (Copy of Rey's Complex Figure, Rey, 1959). The RL/RI-16 reflects memory capacities when effective processing is provided. Participants are presented with a list of 16 words encoded as a function for their semantic category (for example, dentist as a profession). They are then asked to recall all words without semantic cues (free recall) or with the cues used at encoding (cued recall). Learning is repeated over three trials followed by delayed recall 20 minutes later. The third sheet of the Stroop-Victoria was used to assess executive functions where participants were asked to name the color of the ink of incongruent color words (ex: the word blue printed in yellow; Regard, 1981). The score on the copy of the Rey's complex figure was also used as a measure of copy planning and strategy. Participants with MCI

met the criteria proposed by Petersen for the amnestic subtype of MCI (Petersen et al., 2001): 1) presence of a complaint, preferably corroborated by an informant, based on the clinical interview or on performance on a Memory Self-Evaluation Questionnaire (QAM; Van der Linden et al., 1989); 2) performance at least 1.5 SD below the average level of persons of a similar age and educational background based on a standardized memory test (cued and free word recall task: RL/RI-16; Van der Linden et al., 2004) for single domain amnestic MCI, or on standardized memory plus impairment on any of the other non-memory tests included in the neuropsychological assessment for multiple domain amnestic MCI; 3) performance above the age- and education-adjusted threshold for dementia on the MMSE; 4) no significant impact on activities of daily living as reported in clinical interview and measured by the SMAF (Functional Autonomy Measurement System) functional impairment scale. On the basis of these criteria, four of our participants were identified as single domain amnestic MCI and 26 were identified as multiple domain amnestic MCI. As no functional impairment was noted in the SMAF scale and from the clinical interview, none of these participants met the DSM-IV criteria for dementia. Healthy older adults completed the same neuropsychological and clinical protocol as persons with MCI and none of them met the criteria for MCI.

All participants spoke French as their first language. Accordingly, all testing was conducted in French. They all met the following exclusion criteria: diagnosis of probable AD or other form of dementia (for MCI, this was based on clinical criteria prior to referral, based on a medical, neuroradiological, and neuropsychological examination), history of neurological or severe psychiatric disorder, history of cardiovascular disease, alcoholism, drug addiction, using psychoactive drugs or a general anesthesia during the

last six months. This study was approved by the Institut Universitaire de Gériatrie de Montréal Human Ethics Committee.

Tests and Questionnaires

Questionnaires covering psychological health and personality were administered to participants. This was conducted in a single two-hour session by two qualified interviewers (Ph.D. candidates in Clinical Neuropsychology).

Psychological health

The short version of the *Indices de Détresse Psychologique* (Préville, Boyer, Potvin, Perrault, & Légaré, 1992), a French translation of the Psychiatric Symptom Index, was used to measure psychological health (Illfeld, 1976). This 14-item questionnaire measures symptoms of depression, anxiety, and hostility. It has been conceived to evaluate a non-specific symptomatology designated as "psychological distress". Participants are asked if they have experienced, over the past seven days, symptoms described via a 4-point scale ranging from 1 ("never") to 4 ("very often") (norms published by Boyer, Préville, Légaré, & Valois, 1993). The IDPESQ has good internal consistency (Cronbach's alpha coefficient of 0.89; Préville et al., 1992).

The French version of the revised Philadelphia Geriatric Center Morale Scale (PGC-MS; (Lawton, 1975) was used to measure the morale of the participants. This questionnaire includes 17 yes-no questions that cover three main constructs: "agitation",

"attitude toward own aging" and "lonely dissatisfaction". The PGC-MS has been shown to have a good internal consistency (Cronbach's alpha coefficient of 0.85; Lawton, 1975).

Personality

The Eysenck Personality Inventory (EPI) was used to assess personality traits (Eysenck & Eysenck, 1968). The EPI is composed of 57 yes/no questions. It provides information about participants' level of Extraversion-Introversion and Neuroticism-Stability. Both subscales are highly reliable (from .84 to .94; Eysenck & Eysenck, 1968).

The French version of Schwarzer's Generalized self-efficacy scale (GSES) was used to appraise self-efficacy (1994). This questionnaire is composed of 10 statements from which the participants must position themselves on a 4 point scale (e.g., 1 point is given if the statement is judged as entirely false, 4 points if it is evaluated as completely true). The GSES has good internal consistency and reliability (Cronbach's alpha coefficient ranging from 0.76 to 0.90) and a good criteria-related validity.

The Mesure d'actualisation du potentiel (MAP) was used as a measure of self-actualization (Leclerc, Lefrançois, Dubé, Hébert, & Gaulin, 1998). This questionnaire is composed of 27 self-rated items (scored from 1 to 5), each describing typical traits of people who actualize themselves. The final score ranges between 1 (weak actualization) and 5 (strong actualization). The score can be separated into two dimensions 1) reference to self (adaptation and autonomy) and, 2) openness to experience (openness to self, openness to life, and openness to others). The MAP has good internal consistency

(Cronbach's alpha coefficient ranging from 0.86 to 0.89) and reliability (one week retest: $r = 0.87$).

Results

Sociodemographic data

To ensure that groups were well matched on education, age, physical and social functioning, four one-way analyses of variance (ANOVAs) with Group (MCI, Control) as a between-subject factor were performed on age, education, physical health, and social functioning. The analysis did not indicate a main Group effect for age, $F(1,55) = 0.77$, N.S., for education, $F(1,55) = 0.11$, N.S., for physical health, $F(1,55) = 1.97$, N.S., and for social functioning, $F(1,55) = 0.56$, N.S. A chi square analysis revealed that the gender distribution of the two groups did not differ significantly ($x^2 = 2.62$, $p > 0.05$). Nevertheless, gender was used as a covariate in further analyses because gender has been shown to interact with the stability of personality traits in older adults (Small, Hertzog, Hultsch, & Dixon, 2003).

Neuropsychological variables

Tabled 1 shows the mean scores on the cognitive measures for controls and MCIs. In order to reduce the number of variables, control for type 1 errors, increase signal-to-noise ratio and to control for trade off effects in certain tests (ex.: making fewer errors but taking more time), neuropsychological tests were grouped into four composite scores to reflect different cognitive domains: a composite score for the memory cognitive domain, a composite score for the executive domain, a composite score for the visuospatiale domain and an overall score of severity. First, the neuropsychological tasks

were placed on the same scale by calculating individual Z-scores using the mean and SD of the control group as a reference. The memory composite score was obtained using the average Z-scores on RL/RI-16 free recall Trial 3, and RL/RI-16 delayed free recall. The executive composite score was obtained using the average Z-scores on the time and the error score of the Stroop-Victoria (to keep higher Z-scores as indicating higher performance, Z-scores for time and for the number of errors were transformed into negative Z-scores). The visuospatial composite score was obtained using the average Z-scores on the time and the score of the copy of Rey's Complex Figure (to keep higher Z-scores as indicating higher performance, Z-scores for time were transformed into negative Z-scores). The global cognition composite score was obtained using the average Z-scores on the MMSE and MDRS. The results obtained on the composite scores by patients with MCI are -0.61 for Global Cognition, -0.51 for Visuospatial, -0.81 for Executive, and -1.07 for Memory (by definition, the average Z-score of control participants is 0).

One-way ANCOVAs with Group (MCI, Control) as a between-subject factor and gender as a covariate were performed on the composite scores: Global cognition, Visuospatial, Executive, and Memory. As expected, individuals with MCI were impaired relative to controls on all composite scores. A lower level of performance was found in persons with MCI relative to controls on the Global cognition, $F(1,54) = 3.99$, $p = 0.05$, Visuospatial, $F(1,54) = 4.00$, $p = 0.05$, Executive, $(F1,54) = 8.42$, $p < 0.01$, and Memory, $F(1,54) = 5.57$, $p < 0.05$, composite scores.

Psychological health

A one–way multiple analysis of covariance (MANCOVA) with Group (controls, MCI) as a between-subject factor and gender as a covariate was used to compare groups on the psychological health measures. MANOVA is used in designs that have multiple dependent measures likely to be correlated as is the case here. It forms a new dependant variable that is a linear combination of the measured dependant variables. It is a conservative test that reduces the likelihood of type 1 error (Tabachnick, B.G., & Fidell, L.S., 2007). In case of a significant group difference with MANOVA, analyses of the location of the difference can be done by performing ANOVAs on the individual sections. A main Group effect for the MANCOVA was found, $\Lambda = 0.69$, $F(10,45) = 2.06$, $p < 0.05$. A main Group effect was found for the following psychological health measures: PGC-MS (morale), $F(1,54) = 6.80$, $p < 0.05$, depression, $F(1,54) = 8.66$, $p < 0.01$, anxiety, $F(1,54) = 8.14$, $p < 0.01$, and hostility, $F(1,54) = 6.18$, $p < 0.05$. These results indicate that MCI patients have a lower morale and greater depression, anxiety, and hostility than healthy controls (see Table 2).

Personality traits

Five one-way ANCOVAs with Group (MCI, Control) as a between-subject factor and gender as a covariate were used to assess group differences on the neuroticism, extraversion, self-efficacy, reference to self, and openness to experiences scores. No significant group differences were found, $F(1,54) = 2.10$, N.S., $F(1,54) = 1.75$, N.S., $F(1,54) = 0.36$, N.S, $F(1,54) = 0.08$, N.S, $F(1,54) = 0.33$, N.S, for neuroticism, extraversion, self-efficacy, reference to self, and openness to experience, respectively. In

addition, the mean score of each of these scales was within the range of normative values for both groups. In order to control for type 1 errors, only the two personality traits that have been mostly used in the literature (i.e. neuroticism and extraversion) were kept for measures of association.

Associations between cognition, psychological health and personality

Partial correlations (controlling for gender) were calculated between psychological health variables and the neuropsychological composite scores. In MCI persons, significant associations were found between their morale score and their Executive composite score, $r = 0.37$, $p < 0.05$, and between their depression score and their Global Cognition composite score, $r = -0.37$, $p < 0.05$. No association between psychological health and cognitive functions was found in healthy controls (Table 3).

Pearson's partial correlations (controlling for gender) assessed the relation between the two Eysenck personality traits that were measured and the neuropsychological composite scores. As shown in Table 4, the level of neuroticism and of extraversion was not significantly associated with any of our cognitive measures in persons with MCI or in healthy controls.

Finally, the relation between personality and psychological health was assessed by performing partial correlations (controlling for gender) between the two personality traits and the psychological health measures. As shown in Table 5, only neuroticism was associated with the psychological health measures with morale being negatively

correlated with neuroticism and depression, anxiety, and hostility being positively correlated with neuroticism. The association was found to be identical in both groups.

Conclusion

The goal of this study was to shed light on the psychosocial profile of older persons with MCI by assessing personality traits and psychological health. We also measured the associations between personality, cognitive functions and psychological health to verify if personality was related to psychological health in a similar way in MCI as it is in healthy older adults and to assess if personality alterations and psychological disturbances are related to cognitive deficits in MCI.

Participants with MCI exhibited significantly more mood disturbances (depression, anxiety, and hostility) and lower morale than matched healthy older adults. This study is consistent with previous findings indicating reduced psychological health in MCI (Gabryelewicz et al., 2004; Hwang et al., 2004; Kumar et al., 2006; Li et al., 2001; Lopez et al., 2005; Lyketsos et al., 2002). It is worth noting that the aforementioned studies have typically relied on the Neuropsychiatric Inventory (ex.: Hwang et al., 2004; Lyketsos et al., 2002) to assess psychological health. Using different scales, our study provides validity to the assertion that there is reduced psychological health in MCI relative to healthy older adults in spite of the fact that physical health and social functioning were equivalent across both groups. Thus, our findings cannot be related to withdrawal in persons with MCI or reduced interactions with their social or physical environment (i.e. people, experiences).

One of our main findings is that older persons with MCI do not show different personality traits than matched older persons without cognitive deficit. Indeed, no difference in neuroticism, extraversion, self-efficacy, and self-actualization (reference to self and openness to experiences) was found between participants with MCI and a group of healthy older controls matched on socio-demographic factors and recruited from a similar socio-cultural background. Thus, contrary to AD (Aitken et al., 1999; Jacomb & Jorm, 1996; Petry et al., 1989; Strauss & Pasupathi, 1994), MCI is not associated with marked personality changes/disturbances. This is consistent with the absence of prefrontal anomalies in persons with MCI. This finding implies that older persons who seek consultation for their memory problems and experience mild cognitive decline may not be markedly different in terms of their personality than older adults without cognitive deficits. This is important because one might have predicted that people with a high level of neuroticism may be more likely to consult and/or experience cognitive deficits. The findings of the present study do not support this notion and are consistent with previous research indicating that neuroticism is not associated with either current cognitive performance or cognitive decline over a period of 3 years (Jelicic et al., 2003).

One other important finding in MCI was the presence of a negative correlation between their Global Cognition composite score and their depression score and the converging positive correlation between their executive functions composite score and their morale score. Two other studies have shown that the level of depression in MCI is intermediate to healthy older participants and participants with dementia (Li et al., 2001; Lyketsos et al., 2002), a notion confirmed by the results of this study, suggesting that more depressive symptoms are associated with more important cognitive impairment.

No association between personality traits and cognitive performance was found for persons with MCI and healthy older adults. Our results indicating that neuroticism and extraversion are not associated with cognitive performance in older adults are compatible with those of Booth et al. (2006) and Jelicic et al. (2003). The current study extends this finding to older individuals with MCI. Lack of an association between personality traits and cognition in MCI is also consistent with our finding that MCI individuals do not experience personality disturbances.

When measuring the associations between personality and psychological health, it was found that higher neuroticism was related to increased psychological distress and that this was the case in both individuals with MCI and healthy older adults. Thus, although psychological distress is associated with neuroticism in MCI, this relationship is not specific to MCI. Extraversion was not associated with any psychological health variable and again, this was found in both groups. Overall, our results indicate that the association between personality and psychological health in healthy controls is not modified in MCI persons. Again, this is consistent with our finding that personality is not disturbed in these individuals.

It is important to point out some of the limitations of this study. First, our sample (27 healthy older adults and 30 MCI individuals) was relatively small and statistical power may be an issue. However, we do not believe that our results were severely hindered by lack of power because the negative results that we reported were far from significance in the majority of cases. Results that were significant were characterized by

medium to large effect sizes according to Cohen's Standard (Cohen, 1988), with seven of our correlations reaching an r value above 0.50 (r^2 = 0.25; large effect size) and five reaching an r value between 0.30 (r^2 = 0.09) and 0.50 (r^2 = 0.25; medium effect size). By contrast, although we have attempted to reduce the likelihood of type 1 error by using composite scores for cognitive measures, the number of comparisons remain relatively high which could have inflated the risk of type 1 error. However, it is worth noting that the effects we found are consistent with the findings expected on the basis of our initial hypotheses and the results of previous work in older adults. The fact that we recruited our participants with MCI exclusively from memory clinics may be seen as a limitation, as the results cannot be generalized to the general population of cognitively impaired older adults. However, our recruitment strategy bears the advantage that the data are more representative of the population that clinicians from memory clinics will encounter in their daily practice. A third limitation is the use of the Eysenck Personality Inventory to assess personality instead of an instrument that could have measured a larger number of personality traits (such as the NEO PI-R). Thus, future research should be aimed at using more extensive personality tools in the study of personality and MCI. Another limitation is that the design of this study is cross-sectional and not longitudinal. It is therefore impossible to be certain that all MCI will convert to AD and that we did not include individuals with simply poor cognitive functioning rather than with a cognitive decline. It is however important to stress that this limitation should not preclude studying this particular population because in day to day practice, clinicians do not know in advance whether their patient will be among those who will or will not evolve to AD. Also, the fact that we used a cognitive complaint measure may decrease the probability of including individuals with no cognitive decline as cognitive complaints usually comes as

a results of patients noticing a change of cognitive abilities relative to their previous state. Nevertheless, these results need to be replicated in a longitudinal study that will follow MCI until their progression to AD. Finally, it is important to note that correlations do not imply causal links, and hence, our results must be interpreted with caution.

In summary, the goal of the current study was to establish the psychological profile of individuals with MCI and to compare it to that of healthy older adults. We found that MCI individuals do not show personality disturbances, in contrast with what has been reported in persons with AD. Contrary to personality traits, persons with MCI report a significant amount of psychological distress and the magnitude of their depressive symptoms is positively correlated with the severity of their cognitive dysfunction.

The present data have important implication at the clinical level. First, these results indicate that older adults facing cognitive deficits, even if relatively minor, are likely to experience a significant level of psychological discomfort that needs to be acknowledged and properly addressed by clinicians. Second, our findings indicate that the psychological distress experienced by persons with MCI is not merely due to the fact that they belong to a particular type of personality trait like neuroticism. Finally, the importance of the psychological distress reported here by individuals with MCI stresses the relevance of designing interventions, whether pharmacological or non-pharmacological that would target these symptoms. Because of the relation between cognitive symptoms and psychological distress, interventions that would address both

cognitive impairments and psychological distress in a multifactorial manner, are likely to have a synergetic effect in persons with MCI. This could potentially be done by combining psychotherapy and/or pharmalogical medication to cognitive training (Belleville, 2008).

Notes

1. Note that one control was the spouse of an MCI participant and his results on the questionnaires were similar to those of other controls.

Reference

Aitken, L., Simpson, S., & Burns, A. (1999). Personality change in dementia. *Int Psychogeriatr, 11*(3), 263-271.

Arnold, S. E., Hyman, B. T., Flory, J., Damasio, A. R., & Van Hoesen, G. W. (1991). The topographical and neuroanatomical distribution of neurofibrillary tangles and neuritic plaques in the cerebral cortex of patients with alzheimer's disease. *Cereb Cortex, 1*(1), 103-116.

Belleville, S. (2008). Cognitive training for persons with mild cognitive impairment. *Int Psychogeriatr, 20*(1), 57-66.

Booth, J. E., Schinka, J. A., Brown, L. M., Mortimer, J. A., & Borenstein, A. R. (2006). Five-factor personality dimensions, mood states, and cognitive performance in older adults. *J Clin Exp Neuropsychol, 28*(5), 676-683.

Braak, H., & Braak, E. (1991). Neuropathological stageing of alzheimer-related changes. *Acta Neuropathol (Berl), 82*(4), 239-259.

Chetelat, G., Desgranges, B., De La Sayette, V., Viader, F., Eustache, F., & Baron, J. C. (2002). Mapping gray matter loss with voxel-based morphometry in mild cognitive impairment. *Neuroreport, 13*(15), 1939-1943.

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Hillsdale, NJ: Lawrence Earlbaum Associates.

Copeland, M. P., Daly, E., Hines, V., Mastromauro, C., Zaitchik, D., Gunther, J., et al. (2003). Psychiatric symptomatology and prodromal alzheimer's disease. *Alzheimer Dis Assoc Disord, 17*(1), 1-8.

Desrosiers, J., Bravo, G., Hebert, R., & Dubuc, N. (1995). Reliability of the revised functional autonomy measurement system (smaf) for epidemiological research. *Age Ageing, 24*(5), 402-406.

Eysenck, H. J., & Eysenck, S. B. B. (1968). *Manual: Eysenck personality inventory*: San Diego. California: Educational and Industrial Testing Service.

Fillenbaum, G. G., & Smyer, M. A. (1981). The development, validity, and reliability of the oars multidimensional functional assessment questionnaire. *J Gerontol, 36*(4), 428-434.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). Mini-mental state: A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research, 12*(3), 189-198.

Frank, L., Lloyd, A., Flynn, J. A., Kleinman, L., Matza, L. S., Margolis, M. K., et al. (2006). Impact of cognitive impairment on mild dementia patients and mild cognitive impairment patients and their informants. *Int Psychogeriatr, 18*(1), 151-162.

Gabryelewicz, T., Styczynska, M., Pfeffer, A., Wasiak, B., Barczak, A., Luczywek, E., et al. (2004). Prevalence of major and minor depression in elderly persons with mild cognitive impairment--madrs factor analysis. *Int J Geriatr Psychiatry, 19*(12), 1168-1172.

Gauthier, S., Reisberg, B., Zaudig, M., Petersen, R. C., Ritchie, K., Broich, K., et al. (2006). Mild cognitive impairment. *Lancet, 367*(9518), 1262-1270.

Hachinski, V. C., Iliff, L. D., Zilka, E., & et, a. l. (1975). Cerebral blood flow in dementia. *Archives of Neurology, 32*, 317-320.

Hwang, T. J., Masterman, D. L., Ortiz, F., Fairbanks, L. A., & Cummings, J. L. (2004). Mild cognitive impairment is associated with characteristic neuropsychiatric symptoms. *Alzheimer Dis Assoc Disord, 18*(1), 17-21.

Illfeld, F. W. (1976). Further validation of a psychiatric symptom index in a normal population. *Psychological Report, 39*, 1215-1228.

Jacomb, P. A., & Jorm, A. F. (1996). Personality change in dementia of the alzheimer type. *International Journal of Geriatric Psychiatry, 11*, 201-207.

Jelicic, M., Bosma, H., Ponds, R. W., Van Boxtel, M. P., Houx, P. J., & Jolles, J. (2003). Neuroticism does not affect cognitive functioning in later life. *Exp Aging Res, 29*(1), 73-78.

Jorm, A. F., Mackinnon, A. J., Christensen, H., Henderson, S., Scott, R., & Korten, A. (1993). Cognitive functioning and neuroticism in an elderly community sample. *Personality and Individual Differences, 15*(6), 721-723.

Kumar, R., Parslow, R. A., Jorm, A. F., Rosenman, S. J., Maller, J., Meslin, C., et al. (2006). Clinical and neuroimaging correlates of mild cognitive impairment in a middle-aged community sample: The personality and total health through life 60+ study. *Dement Geriatr Cogn Disord, 21*(1), 44-50.

Lawton, M. P. (1975). The philadelphia geriatric center morale scale: A revision. *J Gerontol, 30*(1), 85-89.

Leclerc, G., Lefrançois, R., Dubé, M., Hébert, R., & Gaulin, P. (1998). *Manuel d'utilisation de la mesure de l'actualisation du potentiel*: Centre de recherche sur le vieillissement de l'Institut universitaire de gériatrie de Sherbrooke.

Li, Y. S., Meyer, J. S., & Thornby, J. (2001). Longitudinal follow-up of depressive symptoms among normal versus cognitively impaired elderly. *Int J Geriatr Psychiatry, 16*(7), 718-727.

Lopez, O. L., Becker, J. T., & Sweet, R. A. (2005). Non-cognitive symptoms in mild cognitive impairment subjects. *Neurocase, 11*(1), 65-71.

Lopez, O. L., Jagust, W. J., Dulberg, C., Becker, J. T., DeKosky, S. T., Fitzpatrick, A., et al. (2003). Risk factors for mild cognitive impairment in the cardiovascular health study cognition study: Part 2. *Arch Neurol, 60*(10), 1394-1399.

Lyketsos, C. G., Lopez, O., Jones, B., Fitzpatrick, A. L., Breitner, J., & DeKosky, S. (2002). Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: Results from the cardiovascular health study. *Jama, 288*(12), 1475-1483.

Mattis, S. (1976). Mental status examination for organic mental syndrome in the elderly patient. In L. Bellak & T. B. Karasu (Eds.), *Geriatric psychiatry*. New York: Grune & Stratton.

Meier, B., Perrig-Chiello, P., & Perrig, W. (2002). Personality and memory in old age. *Aging, Neuropsychology and Cognition, 9*(2), 135-144.

Meins, W., & Dammast, J. (2000). Do personality traits predict the occurrence of alzheimer's disease? *Int J Geriatr Psychiatry, 15*(2), 120-124.

Modrego, P. J., & Ferrandez, J. (2004). Depression in patients with mild cognitive impairment increases the risk of developing dementia of alzheimer type: A prospective cohort study. *Arch Neurol, 61*(8), 1290-1293.

Pennanen, C., Testa, C., Laakso, M. P., Hallikainen, M., Helkala, E. L., Hanninen, T., et al. (2005). A voxel based morphometry study on mild cognitive impairment. *J Neurol Neurosurg Psychiatry, 76*(1), 11-14.

Petersen, R. C., Doody, R., Kurz, A., Mohs, R. C., Morris, J. C., Rabins, P. V., et al. (2001). Current concepts in mild cognitive impairment. *Arch Neurol, 58*(12), 1985-1992.

Petersen, R. C., Smith, G. E., Waring, S. C., Ivnik, R. J., Tangalos, E. G., & Kokmen, E. (1999). Mild cognitive impairment: Clinical characterization and outcome. *Arch Neurol, 56*(3), 303-308.

Petry, S., Cummings, J. L., Hill, M. A., & Shapira, J. (1989). Personality alterations in dementia of the alzheimer type: A three-year follow-up study. *J Geriatr Psychiatry Neurol, 2*(4), 203-207.

Préville, M., Boyer, R., Potvin, L., Perrault, C., & Légaré, G. (1992). La détresse psychologique: Détermination de la fiabilité et de la validité de la mesure utilisée dans l'enquête santé québec. Enquête santé québec 1987+. (Vol. Cahier de Recherche No 7): Ministère de la Santé et des Services sociaux Gouvernement du Québec.

Regard, M. (1981). Cognitive rigidity and flexibility: A neuropsychological study: University of Victoria, Canada.

Rey, A. (1959). *Test de copie d'une figure complexe: Manuel*. Paris: Les éditions du centre de psychologie appliquée.

Robert, P. H., Berr, C., Volteau, M., Bertogliati, C., Benoit, M., Sarazin, M., et al. (2006). Apathy in patients with mild cognitive impairment and the risk of

developing dementia of alzheimer's disease a one-year follow-up study. *Clin Neurol Neurosurg*.

Roberts, B. W., & DelVecchio, W. F. (2000). The rank-order consistency of personality traits from childhood to old age: A quantitative review of longitudinal studies. *Psychol Bull, 126*(1), 3-25.

Schwarzer, R. (1994). Generalized self-efficacy: Assessment of a personal coping resource [german]. *Diagnostica, 40*(2), 105-123.

Small, B.J., Hertzdog, C., Hultsch, D.F., & Dixon, R.A. (2003). Stability and change in adult personality over 6 years : findings from the Victoria Longitudinal Study. *J Gerontol B Psychol Sci Soc Sci, 58*(3), P166-176.

Steunenberg, B., Beekman, A. T., Deeg, D. J., & Kerkhof, A. J. (2006). Personality and the onset of depression in late life. *J Affect Disord, 92*(2-3), 243-251.

Strauss, M. E., & Pasupathi, M. (1994). Primary caregivers' descriptions of alzheimer patients' personality traits: Temporal stability and sensitivity to change. *Alzheimer Dis Assoc Disord, 8*(3), 166-176.

Talassi, E., Cipriani, G., Bianchetti, A., & Trabucchi, M. (2007). Personality changes in alzheimer's disease. *Aging Ment Health, 11*(5), 526-531.

Van den Heuvel, N., Smits, C. H., Deeg, D. J., & Beekman, A. T. (1996). Personality: A moderator of the relation between cognitive functioning and depression in adults aged 55-85? *J Affect Disord, 41*(3), 229-240.

Van der Linden, M., Adam, S., Agniel, A., Baisset-Mouly, C., Bardet, F., Coyette, F., et al. (2004). *L'évaluation de troubles de la mémoire: Présentation de quatre tests de mémoire épisodique (avec étalonnage)*. Marseille: Solal.

Van der Linden, M., Wijns, C., Von Frenkell, R., Coyette, F., & Seron, X. (1989). *Un questionnaire d'auto-évaluation de la mémoire (qam)*. Bruxelles: Editest.

Whitwell, J. L., Przybelski, S. A., Weigand, S. D., Knopman, D. S., Boeve, B. F., Petersen, R. C., et al. (2007). 3d maps from multiple mri illustrate changing atrophy patterns as subjects progress from mild cognitive impairment to alzheimer's disease. *Brain, 130*(Pt 7), 1777-1786.

Yesavage, J. A. (1988). Geriatric depression scale. *Psychopharmacological Bulletin, 24*, 709-711.

Acknowledgement

The authors report no conflicts of interest. This study was supported by a grant from the REPAR\FRSQ and from the Canadian Institutes of Health Research (CIHR) to Sy.B. Furthermore, Sy.B. was supported by a Chercheur national fellowship from the Fond de la Recherche en Santé du Québec (FRSQ), FC was supported by a scholarship from the Fond Québécois de la Recherche sur la Nature et les Technologies (FQRNT); Sa.B. by a doctoral scholarship from FRSQ and from the Alzheimer Society of Canada, and VC by a doctoral scholarship from the Canadian Institute of Health Research (CIHR). We thank Anne Guérette and Lise Gagnon for their participation in the earlier part of this project, Dr Serge Gauthier for referring the participants, Émilie Lepage for the neuropsychological evaluation of the participants and Luke Henry and Janet Boseovski for editorial assistance.

xc

Table 1

Mean scores on the cognitive measures for controls and MCIs. S.D. are in parentheses.

Cognitive domain	Test	Controls	MCIs
General	MDRS	140.26 (3.12)	137.03 (5.28) **
	MMSE	28.89 (0.97)	28.63 (1.16)
Executive Functions			
	Stroop color time (plate 3)	27.34 (8.68)	33.35 (11.45) *
	Stroop color errors (plate 3)	1.07 (1.30)	2.27 (2.35) *
Visuospatial			
	Copy of Rey's Figure (time)	199.41 (76.56)	249.89 (154.30)
	Copy of Rey's Figure (score)	31.39 (5.22)	29.55 (4.80)
Memory			
	RL/RI-16 free recall trial 3	11.52 (2.05)	9.33 (3.34) **
	RL/RI-16 delayed free recall	12.33 (2.17)	10.03 (3.68) **

Note. * $p < 0.05$. ** $p < 0.01$.

Table 2.

Level of psychological health among controls and MCIs. S.D. are in parentheses.

	Controls	MCIs
PGC-MS: Morale	14.41 (2.45)	12.50 (3.83) *
PSI:		
Depression	1.44 (1.83)	2.87 (2.11) **
Anxiety	1.44 (1.19)	2.80 (2.41) *
Hostility	1.30 (1.84)	2.47 (2.16) *

Note. * $p < 0.05$. ** $p < 0.01$.

Table 3.

Correlations between composite scores and psychological health for controls and MCIs.

	Global Cognition		Visuo spatial		Executive		Memory	
	MCI	Control	MCI	Control	MCI	Control	MCI	Control
PGC-MS: Morale	0.30	0.13	0.25	-0.19	0.37 *	0.11	-0.04	0.18
PSI:								
Depression	-0.37 *	-0.11	-0.11	-0.06	-0.15	-0.04	-0.13	-0.38
Anxiety	-0.08	-0.10	-0.01	0.11	-0.26	0.21	-0.06	0.21
Hostility	0.10	0.06	0.11	0.15	-0.03	0.28	0.22	-0.14

Note. * $p < 0.05$.

Table 4.

Correlations between composite scores and personality traits for controls and MCIs.

	Neuroticism		Extraversion	
	MCIs	Controls	MCIs	Controls
Global Cognition	0.05	0.09	0.10	0.24
Visuospatial	0.01	0.16	0.25	0.14
Executive	0.20	0.07	0.22	0.08
Memory	0.01	0.05	0.12	0.11

Table 5.

Correlations between personality traits and psychological health for controls and MCIs.

	Neuroticism		Extraversion	
	MCIs	Controls	MCIs	Controls
PGC-MS: Morale	-0.64 ***	-0.61 ***	0.25	0.11
PSI:				
Depression	0.45 *	0.55 **	-0.18	-0.17
Anxiety	0.60 ***	0.57 **	0.04	-0.00
Hostility	0.67 ***	0.51 **	0.01	-0.14

Note. * $p < 0.05$. ** $p < 0.01$. *** $p < 0.001$.